New Orleans Medical
and
Surgical Journal

$4.00 Per Annum, 35c Per Copy
Vol. 103, No. 10

APRIL, 1951

Published Monthly
1430 Tulane Avenue, New Orleans 12, La.

FALLACIES IN CURRENT THERAPEUTIC TRENDS IN ACUTE APPENDICITIS*†

FREDERICK FITZHERBERT BOYCE, M. D.

NEW ORLEANS

In a continuing study of acute appendicitis at the New Orleans Charity Hospital, which was begun in 1933, 7,613 cases have been collected, covering a period of almost twenty years and analyzed in seven series. The latest analysis covers the years 1946-1949 inclusive. The mortality for the entire series was 4.46 per cent (340 fatal cases), but the serial mortality has declined successively from 6.58 per cent for the first series to 1.7 per cent for the latest.

In view of the significant decline in the case fatality rate, it seems curious that the investigation of the last 1,172 cases of acute appendicitis should have left me with a very distinct feeling of uneasiness. The explanation is a number of trends which were evident in this series and which seem to me neither reasonable nor safe. They suggest, in fact, that all is not as well in this disease as the greatly decreased mortality might suggest.

MORTALITY ACCORDING TO RACE AND AGE GROUP

The case fatality in the 734 patients from 13 to 39 years of age in the latest series studied was exactly the same in both negro and white patients, 0.27 per cent. But all 3 deaths in children occurred in negroes, while in the group of patients 40 years of age and over, the negro mortality was half as high again as the white.

There were only 2 deaths in the 734 patients in this series who were between 13 and 39 years of age, and only 3 in the 236 children up to 12 years of age. But there were 15 deaths, 7.42 per cent, in the 202 patients 40 years of age and over, which is very nearly six times higher than the case fatality rate in young children, and more than 27 times higher than the case fatality rate in the adolescent and young adult group. There is still no reason to be complacent, therefore, about acute appendicitis in negroes or in persons in the upper age brackets.

INCIDENCE OF COMPLICATED DISEASE

In the second place, although the case fatality rate in the seventh and last series of cases of acute appendicitis analyzed from the New Orleans Charity Hospital was almost half as low as the rate in the sixth series, the seventh series contained a larger number of complicated cases than the sixth series. A statistician might regard the difference as insignificant. I do not. Clinically, every case of acute appendicitis that progresses from a simple to a complicated status increases the potentialities for mortality and also enhances the likelihood of morbidity, a factor which, as I shall point out shortly, is of considerable importance.

The higher proportion of complicated cases of acute appendicitis in the most recent series is not hard to explain. One reason is that almost half (47 per cent) of the

*From the Department of Surgery, Tulane University of Louisiana School of Medicine, and Charity Hospital of Louisiana at New Orleans.

†Presented at meeting of the Third District Medical Society, at New Iberia, Louisiana, January 24, 1951.

patients failed to enter the hospital until after the first twenty-four hours of illness, the most favorable period, had passed. Another reason is that more than a third of the patients had taken purgatives, including 18 who had taken them on the advice of the physicians whom they had consulted.

The dangers of purgation in acute appendicitis have been recognized since Fitz pointed them out in his classic description of the disease in 1886. It is disconcerting, therefore, sixty-five years later, to find such a proportion of patients treating themselves, or being treated, for abdominal pain in this manner. It is even more disturbing to find that proportionately more purgatives were taken in the last series of cases than in the preceding series, and that proportionately more were given by physicians. In a few instances if the patients are to be believed, their physicians mentioned acute appendicitis among the diagnostic possibilities before the purgative was ordered. These remarks take no account of the numerous enemas ordered by physicians, nor of the icebags which have again come to the fore as a method of treatment in this disease.

ATYPICAL ACUTE APPENDICITIS

In the third place, it does not seem to me that this last series of cases shows as general an appreciation of the atypical character of acute appendicitis as has been displayed in some of the earlier series. Some of the notations on the charts make that clear: "The picture which this patient presents is not consistent with acute appendicitis." "The high fever is this case would seem to rule out acute appendicitis." "Since this patient has a previous history of a conservatively treated appendiceal abscess, he should merely be observed." "The diagnosis in this case is only 40 per cent acute appendicitis." "Since acute appendicitis cannot positively be ruled out, this patient should be re-evaluated at the end of twelve hours."

The patient who had only 40 per cent acute appendicitis was not admitted to the hospital when he first applied. He returned twenty-four hours later with a ruptured appendix. The patient who had too high fever to have acute appendicitis also had a ruptured appendix when he was finally operated on, and so did a good many others about whom similar remarks were made. Residents who are talking about acute appendicitis in this manner (in all fairness I should say that they come from many widely scattered medical schools) have quite evidently not been taught the facts as they concern this disease. No one who reads, as I have read, many thousands of histories of this condition can ignore the fact, even allowing for historical error, that acute appendicitis is an atypical disease in a very fair proportion of cases.

THE TIMING OF OPERATION

Since acute appendicitis is so often an atypical disease, the only safe plan of management would seem to be to operate in any suspected case, after every reasonable diagnostic effort has been made, and to perform the exploration without undue delay. Twelve hours is much too long to wait to "re-evaluate" a patient suspected of having this disease. Most authorities believe that six hours is the top limit of safety for observation, and teach that operation should be performed at the end of this time if one cannot say positively that the patient does *not* have acute appendicitis. For my own part, I fully agree with Wangensteen that exploration is justified even if the only symptoms and signs present are abdominal pain and right-sided tenderness which cannot positively be explained by some other cause.

In the January 1951 issue of the *Archives of Surgery* there is a surgical forum on the timing of operation in acute appendicitis. The surgeons who participated in it recognized the possibility of error when the plan of prompt exploration was followed, their estimates varying from 10 to 33 per cent. Three of the surgeons who set the percentage of error high justified it as part of a deliberate policy. In their experience, when the error was much below 33 per cent there was a strong possibility that many patients who actually had acute appendicitis might not be operated on. They justified the error—to themselves, to the patients, and to

the patients' families—on the ground of avoiding the greater error of failing to operate for a potentially perforating lesion. I quite agree that there is every justification for what one might call unnecessary emergencies in the management of acute appendicitis, though I cannot agree that the error of 33 per cent is either usual or justified. I am disturbed to find, however, that in the last series of cases studied from Charity Hospital, whether from fear of error or from a new sense of complacency about this disease, there was a far greater tendency to delay operation and to observe the patient for hours or even days than there had been in other series.

SURGICAL AND ADJUNCT THERAPY

The question naturally arises why, in view of the numerous factors of mortality which have just been analyzed, the mortality in acute appendicitis has continued to decline. The explanation is simple: The patients are being saved by the treatment they receive after they are once hospitalized. They owe their lives not only to good surgery, but to intensive supportive therapy, and to chemotherapy and antibiotic therapy. But it seems upside-down, Alice-in-Wonderland thinking to delay and watch complacently while patients progress to a state from which they must be rescued by these means. It would be far more reasonable to treat them in the early stages of their disease, when simple appendectomy and very little else will cure them promptly, and without any complications at all. The main point of these remarks, in fact, is that we would do well to re-evaluate our use of the sulfonamides and the antibiotics.

In the (fifth) series of cases of acute appendicitis which I analyzed from Charity Hospital, in 1941, the sulfonamides were used in a certain number of cases, but there was no consistency about usage, let alone dosage or route of administration. In the (sixth) series analyzed in 1945, the sulfonamides were used consistently in complicated cases, frequently in uncomplicated cases, and usually according to a fairly well standardized dosage pattern. By the end of this series the intraperitoneal route was being used only occasionally. Penicillin had become available for general use and was being administered quite frequently, often in combination with a sulfonamide, though the dosage was widely variable.

In the 1,172 cases of acute appendicitis analyzed for the four-year period ending in 1949, the general use of these new agents was the outstanding therapeutic trend. Streptomycin had become available, and as time passed, it was almost the universal practice to employ combined chemotherapeutic and antibiotic therapy. A sulfonamide, penicillin, and streptomycin were usually used in combination, and in the later years of the analysis aureomycin was sometimes added. This method of treatment was routine in the complicated cases and was used quite frequently in the uncomplicated cases. Intraperitoneal administration was seldom employed. The dosage of all drugs was usually ample, at least in the complicated cases. In some of the uncomplicated cases it is doubtful that enough of any single drug was given to produce any significant effect, and, as is unavoidable, some of the more seriously ill patients died before they had received enough treatment to alter the course of their illness: It is impossible, however, because of the variety of agents, dosages, routes of administration and combination of methods, to present a statistical picture of the chemotherapeutic and antibiotic therapy used in this series of cases. Other observers report the same impasse.

It should be said at once that there is little doubt that these agents were responsible for numerous almost incredible recoveries which certainly could not have occurred ten years ago, or even five years ago. But let us not attribute the whole responsibility for these results to them. It should be remembered—as it frequently is not—that just about the time these drugs first became available, the full peritonitis regimen began to be practised routinely in complicated cases, not haphazardly, and that it also began to be used prophylactically, not after the need for it became

evident or as formerly, in some instances, after the patients were almost moribund.

From the standpoint of adjunct therapy the patients in this last series, as in preced-in gseries, were treated excellently. Preparation for operation was almost invariably good. The majority of patients, even those with simple acute disease, were given infusions while they were being worked up. Transfusion was used more liberally in the last series than in the preceding series. In both series intestinal decompression and oxygen therapy were seldom omitted when they were indicated. Deaths from thrombosis and embolism almost never occurred because prodromal signs were searched for, and because such precautions were instituted as bandaging the extremities, early ambulation, and prophylactic ligation of the femoral vein whenever there was need for them. In short, while giving due credit to the newer drugs, let us not forget the importance of this supportive regimen and let us assign to it the proper credit for its role in the reduction of the mortality of complicated acute appendicitis. Moreover, let us not credit the new agents for the recoveries in uncomplicated cases which would have occurred with exactly the same smoothness and rapidity if they had not been administered at all.

The main point at issue, however, is not the unnecessary use of these antibiotics but the fact that they are being employed in ways that can be described only as unwise and imprudent. Among these 1,172 patients, for instance, were 83 who had been treated outside of the hospital by drugs which were positively stated to be, or which could be assumed to be, either sulfonamides or antibiotics. Some patients were treated at home by these means for as long as twenty-one days. Some, even more surprisingly, were given these drugs as early as five or six or eight hours after the onset of symptoms and signs which, from the patients' descriptions, fitted the classic picture of acute appendicitis. An occasional patient, receiving no benefit from the prescription of the first physician called, consulted a second, who treated him with more of the same drugs. One child was given penicillin at home within two hours of the onset of abdominal pain. Later he was moved to a private hospital, where he was treated by penicillin and aureomycin until the family funds were exhausted. Six days after he became ill he underwent appendectomy at Charity Hospital. In spite of continued antibiotic and sulfonamide therapy, the wound became infected and necrotic, partial dehiscence occurred, and drainage and secondary closure were necessary. Still later, a culdesac abscess required incision and drainage, and six months after the original illness an incisional hernioplasty was necessary. This story is not the only one of the kind in the last series of cases.

The contagion of this type of therapy—the description seems fair enough—spread to the hospital admitting room, and 39 of the 1,172 patients were not admitted to the hospital when they applied. Instead, they were given prescriptions, usually for a sulfonamide, and were told to rest in bed at home. If this advice was intended to institute conservative therapy, it was obviously a modification never dreamed of by the originators of the method.

Some of the patients who were refused admission when they first applied were not thought to have acute appendicitis. Others, who had been treated at home by these means, when they were finally admitted were treated for conditions other than acute appendicitis because the use of chemotherapy and antibiotic therapy had masked the symptoms and distorted the clinical picture of acute appendicitis.

DELAYED SURGERY IN COMPLICATED ACUTE APPENDICITIS

The delays in surgery which occurred in many of these cases in the hospital must also be attributed to unthinking faith in the new drugs. I happen, myself, not to approve of the conservative method of treating acute appendicitis, but I doubt that many of its advocates would favor so strict an application of it that a patient who was already anesthetized was not operated on because it was thought a mass had been palpated in the abdomen, or that an abscess found at laparotomy was left undisturbed

and without drainage in the name of conservatism.

The whole question of delayed operation in acute appendicitis has come to the fore again because physicians are putting so much faith in the sulfonamides and the antibiotics. That is frankly stated in the surgical forum in the January 1951 *Archives of Surgery*, to which reference has already been made. The majority of the editors who undertook to settle the question were in favor of prompt operation and were against the policy of deferring appendectomy until the process subsides. I agree with them, for at least five good reasons:

1. The diagnosis of rupture of the appendix is notoriously inaccurate. A localized mass may quite as well be an inflamed appendix surrounded by intestines and omentum as an appendiceal abscess. It is unfortunate, I think, that the editors of the *Archives of Surgery* did not enlarge upon this possibility in their discussion.

2. It is impossible, even when an unmistakable peritonitis exists, to say definitely that the process is spreading or is localizing, and equally impossible, while the source of the infection remains in situ, to predict with certainty that an apparently subsiding peritonitis will not reverse its trend.

3. The danger may be remote, but it nonetheless exists, that a localized abscess may rupture intraperitoneally. More often than not this is a catastrophe which terminates fatally.

4. It is against all reason to argue that the continued entrance into the peritoneal cavity of infection from a ruptured viscus is safer than the performance of a properly planned and skilfully executed surgical procedure which removes the source of the infection.

5. The results of conservative therapy are no better than the results of prompt surgery. It is doubtful, as a matter of fact, if they are as good, because this method is applied only in a carefully selected group of patients, many of whom are never very ill.

THE LIMITATIONS OF CHEMOTHERAPY AND ANTIBIOTIC THERAPY

Most of the patients in the recent Charity Hospital series survived, including most of those in the upper age brackets, even if they were treated conservatively for more or less long periods of time, and chemotherapy and antibiotic therapy certainly had much to do with their survival. But a good many of them survived only after passing through many and great dangers. Among the 202 patients over 40 years of age, for instance, only 69 had simple acute disease. Most of these recovered uneventfully. But there occurred in the other patients in this age group, in spite of the new methods of treatment, 40 wound infections, 18 serious enough to require incision and drainage or debridement; 7 eviscerations, 2 of which were fatal; 7 fecal fistulas, 1 of which was fatal; 5 culdesac abscesses; 4 subphrenic abscesses; 1 other residual abscess; and 3 intestinal obstructions, 2 of which were late complications. This is a larger proportion of complications than occurred in most of the series of cases of acute appendicitis treated at the New Orleans Charity Hospital before the introduction of the sulfonamides and antibiotics.

While we utilize to the fullest the amazing curative and protective properties of these new drugs we would do well to face frankly their limitations and disadvantages:

1. They do not furnish any protection against the development of acute appendicitis. In this last Charity Hospital series the disease occurred in a child who was under penicillin therapy for bronchiectasis and in 2 adult patients, 1 of whom died, while they were under penicillin therapy for syphilis.

2. These drugs are blood-borne and are correspondingly ineffective in areas in which the circulation is inadequate. They cannot be relied upon, therefore, in gangrenous processes and localized, walled-off abscesses. In this type of case much of the success attributed to them should probably be attributed to the supportive measures used with them.

3. They are ineffective unless they are used in adequate amounts and over sufficiently long periods of time. As many cases in this series showed, the infection promptly becomes active again when they are discontinued too soon.

4. Complications after operation may be masked in patients who are receiving heavy antibiotic therapy. In some cases at Charity Hospital patients were operated on one or more times for the complications of acute appendicitis before the appendix was recognized as the original source of the trouble.

5. There seems no reason for using these agents in the average uncomplicated case of simple acute appendicitis. Some of them, if they are used unwisely, may cause the growth of resistant strains of organisms. They are not, any of them, entirely free from risk, and some of them may give rise to serious reactions. They increase the burden of medical and nursing care. Some of them are still very expensive, which makes them a hardship on the patient or, if he is indigent, creates an unnecessary drain on the public purse. I cannot bring myself to accept the concept, which I have heard seriously advanced, that surgeons who do not order these drugs in all surgical cases, whether or not they are needed, may find themselves with suits for malpractice on their hands if unexpected complications should develop.

6. The basic error in much of the present use of the sulfonamides and antibiotics in acute appendicitis is failure to remember the still incontrovertible fact that a pus-containing lesion is a surgical lesion, and that all drugs are adjuncts to, not substitutes for, surgical procedures conducted according to sound surgical principles. The corollary of this concept is that the best treatment for acute appendicitis is still prompt appendectomy.

SUMMARY

An analysis of 1,172 cases of acute appendicitis treated at the New Orleans Charity Hospital for the four-year period ending in 1949 reveals certain trends which indicate an undue reliance upon measures other than prompt surgery. In particular, sulfonamide and antibiotic agents were sometimes used, both inside and outside of the hospital, as if they were curative rather than adjunct agents. A tendency toward the wider use of delayed or expectant treatment was also observed in this series, chiefly because of the reliance placed upon these drugs. It is suggested that their use be re-evaluated, that they be used only when they are indicated, and that their limitations as well as their undeniable powers be taken into account when they are prescribed.

SYMPOSIUM ON CANCER

PRINCIPLES OF THE SURGICAL TREATMENT OF CANCER

PAUL T. DeCAMP, M. D.

NEW ORLEANS

With rapid advances in radiation therapy, introduction of radioactive technics, and development of chemical and hormonal therapy, it becomes necessary to reconsider the underlying philosophy and basic principles which have made surgical excision the most beneficial treatment of cancer. Improvements in management of the surgical patient have widely extended the safety of surgical procedures. Removal of restrictions on the magnitude of operative procedures makes it necessary to consider the scope of each operation in order to balance the possible additional benefit to some, against the increased disability to all, attendant upon more radical technics. For this and other reasons there have been repeated recommendations that surgical technics be altered.

Ultimate appraisal of any therapeutic method must rest solely on results obtained following its application, but cancer is such a lethal and protean disease that such appraisal requires years at best and final de-

Presented at meeting of the Orleans Parish Medical Society, October 9, 1950.

From the Departments of Surgery, Ochsner Clinic and Tulane University of Louisiana, School of Medicine, New Orleans.

cisions are frequently inconclusive. Well considered judgment based on sound surgical principles will usually enable accurate prediction of the type of response to be anticipated from a specific procedure.

The basic tenet of the surgical treatment of cancer is simple—that benefit can be obtained if the entire cancerous lesion can be excised without too serious injury to the patient. The present generally poor results following surgical treatment of cancer are evidence of the difficulties encountered in applying this simple premise. Failures result from inadequate surgical therapy or application of treatment after the disease is so far advanced that the entire lesion cannot be removed. Effective surgical treatment is completely dependent upon diagnosis when the neoplasm is still localized. This is a responsibility of the entire profession and the general practitioner in particular.

It is often difficult for the surgeon to understand why there has been so much delay before a patient is sent to him for treatment. Again and again, he experiences the desperate sense of frustation as he views the malignant tissues already extended beyond the reach of his scalpel, and he wonders what the end might have been had the patient come to him two instead of ten months after the onset of symptoms. Because of the crucial significance of such delays it is well to consider their causes.

In this era of fund-raising campaigns and such slogans as, "one in eight will die of cancer," one rather expects to find a cancer around every corner. Actually, in unselected general practice a new case of cancer will be encountered only once in several hundred patients. There are hundreds of patients with respiratory infections for each patient with cancer of the lung. The malignant dyspepsia is hidden among scores of its nonmalignant fellows. Carcinoma of the colon often causes constipation, but constipation is well-nigh universal. The low case incidence of cancer must be recognized to understand the difficulty in keeping the index of cancer suspicion not only high but durable.

Diagnostic problems are increased by the fact that the symptoms of curable cancer are rarely distinctive. The mammary cancer is only a lump, the gastric lesion indigestion, the colonic neoplasm constipation and the pulmonary malignancy a cough or thoracic discomfort. It is only by awareness of the age and sex predilection for a given type of cancer, and alertness to the persistence of symptoms, that a more thorough examination will be made and cancer discovered at a time when surgical therapy can be effective. Many internal cancers are accessible to digital or endoscopic examination and by such means a definitive diagnosis may be promptly made.

Since many types of cancer are not manifested clinically until far advanced, we cannot wait until symptoms appear to treat the patient. For this reason every effort must be made by routine physical examinations, screening methods, and periodic check-ups to discover cancer at the earliest possible stage. There seems little doubt, for instance, that the majority of cases of bronchogenic carcinoma are radiologically visible for some months before they become symptomatic. Such detection is arduous and the incidence of cancer so discovered is low so that faith, patience, and persistence are required. However, the high incidence of cures obtained in the early lesions thus discovered is ample reward.

An additional diagnostic problem encountered by the entire profession is the frequent inability to establish the identity of an early malignant lesion in an organ without an exploratory operation. For example, the lump in the breast must be removed and examined microscopically to establish the diagnosis of carcinoma. In many cases of cancer of the stomach laparotomy is essential to establish the character, or even the presence, of the gastric lesion. Even with the aid of cellular studies of sputum and bronchial washings, 25 per cent of cases of bronchogenic carcinoma require exploratory thoracotomy for diagnosis. This problem will increase as more early cases are discovered. It is imperative that principles be established for the management of

patients under these circumstances. Unless asymptomatic or obscure lesions are to be pursued relentlessly until they are extirpated or definitely established as benign, there is no point in efforts to discover such early lesions.

The type of surgical attack on a cancerous growth is the surgeon's problem but the profession as a whole must understand and criticize his recommendations. In his decisions the surgeon is governed by a certain philosophy together with knowledge of the pathologic course of the disease. As successful surgical treatment demands removal of all cancerous tissue, it is imperative that the surgeon understand the nature of the growth and its tendency to extend to other parts of the same organ and adjacent tissue, as well as its pattern of lymphatic and vascular metastasis. Careful observation of clinical results following operative procedures, and the location and character of postoperative recurrences, determine the desirable limits of surgical extirpation.

The surgeon has but a single reasonable opportunity to cure a patient with cancer. Block excision of the primary lesion and the areas of metastasis is the procedure of choice. The Halstead radical mammectomy for carcinoma of the breast is a good example of this type of procedure. The entire organ, a wide area of surrounding tissue, and the entire axillary contents are removed in a single block. The suggestion has been made that regional node dissection be carried further by mediastinotomy and dissection along the internal mammary vessels, or by extensive excision of supraclavicular tissues. These maneuvers are discontinuous dissections, and it is unlikely that metastases having spread that far will not have spread further. Halstead himself studied the effect of removal of supraclavicular lymph nodes and came to the conclusion that this procedure offered no significant additional benefit.

In the presence of bronchogenic carcinoma prudence demands removal of the entire lung and the contiguous nodes of the mediastinum. True *en bloc* excision is unfortunately impractical. Elective lobectomy for peripheral lesions does not appear to be sound, since regional lymph node excision cannot be as effective. There is need for more accurate pathologic knowledge concerning the spread of lesions to adjacent lobes and to hilar and mediastinal nodes.

Vigorous application of the principles of wide local excision combined with *en bloc* resection of regional lymph nodes has resulted in a significant number of five-year survivals of patients with malignant melanomas. A completely pessimistic attitude has been rendered obsolete by the bold application of sound principles.

Moderately effective regional gland dissections have been performed with large wedge resections of malignant lesions of the colon. The recent emphasis on much wider resection of the bowel, e. g., left hemicolectomy, permits inclusion of a much greater area of proximal nodal spread without increased hazard or discomfort to the patient. It is anachronistic that at the same time there should be renewed agitation to constrict the range of resection of rectosigmoidal lesions to preserve the anal sphincter. This is unsound in principle and tragic in practice.

Certain surgeons are recommending total gastrectomy for all resectable cases of carcinoma of the stomach. The argument that removal of the entire organ is essential for adequate local excision and for complete regional node dissection is basically sound, and governs the surgical treatment of cancer in many organs. However, extension from subtotal to total gastrectomy considerably increases the morbidity and mortality rates. The help of the pathologist must again be obtained to determine how frequently the recurrence of carcinoma following subtotal resection is due to recurrence within the resectable area of total gastrectomy as against more distant metastasis. An accurate understanding of the course of the disease and the mode of spread is again essential to proper application of surgical therapy.

There are circumstances under which surgical treatment is beneficial even though it cannot be considered curative. In general,

if distant metastases have occurred, the disease is too far advanced to warrant surgical attack on the primary lesion. Operation is almost never attempted in the face of incontrovertible evidence of distant spread. The situation is altered, however, if incurability is determined only at the time of operation. Resection of the primary lesion is often indicated under such circumstances, since considerable symptomatic benefit may be obtained by removal of a large, obstructing, bleeding, infected carcinomatous mass. Palliative removal of a lesion in the lung, stomach, or large intestine frequently adds much to the comfort of the patient and possibly prolongs life. Palliative operative procedures, such as gastroenterostomy, in which the primary lesion is not removed, are much less effective and have generally proved to be unsatisfactory. It is sometimes beneficial to remove a late-appearing solitary metastatic lesion of a growth which characteristically metastasizes only sporadically.

Surgical procedures on the nervous system for relief of intractable pain are indicated when the course of the disease is apt to be long. Procedures, such as rhizotomy, prefrontal lobotomy, and topectomy, have definite, though limited, indications in the treatment of patients with cancer.

SUMMARY

In the face of new therapeutic methods and repeated recommendations for alterations in existing surgical technics it is desirable to review the principles underlying the surgical treatment of cancer. Curative treatment depends on extirpation of all neoplastic tissue. The limits of practical surgical endeavor are set by knowledge of the pathologic extension of the neoplastic disease and the expected postoperative health and comfort of the patient.

Treatment of patients early in the course of the disease is possible only by prompt referral of the patient with symptoms, and determined efforts to detect cancer when it is still asymptomatic. Vigorous application of well considered radical surgical procedures at this stage results in the most effective control of cancer.

HORMONES IN CANCER THERAPY

ALBERT SEGALOFF, M. D.

NEW ORLEANS

My predecessors on this symposium have referred to methods which offer varying degrees of hope for the cure and eradication of cancer. At least at present hormonal therapy has nothing to offer which could be classified as cures or eradication. Rather we must speak in terms entirely of palliation, regression, increased survival times, and comfort. Although the future may hold some hope of attainment of cure through hormonal agents, it is better to deal with the present realities.

The current glamourous agents of endocrinology, cortisone (compound E) and ACTH (the hypophyseal adrenocorticotropic hormone), have, of course, been tested for their effects on neoplastic disease and have indeed shown promise in some types of malignancy. For practical purposes ACTH and cortisone will be considered as a single entity since the adrenocorticotropic hormone has its effect in various diseases by stimulating the adrenal to produce either cortisone or cortisone-like substances. Except in an occasional instance it has not been possible to differentiate between the actions of these two agents. Although there is evidence that the administration of ACTH leads to the secretion by the adrenal of predominantly compound F, its actions can still not be readily distinguished from that of cortisone.

Some years ago Dougherty and White[1] described the lympholytic effect of excess adrenal hormone, either administered exogenously or from the animal's own adrenal under stimulation with ACTH. Essentially the same effects have been described for the increased adrenal secretion associated with the general adaptation syndrome of Selye.

Presented at meeting of the Orleans Parish Medical Society, Oct. 9, 1950.

From the Department of Medicine, Tulane University School of Medicine and the Endocrine Research Laboratories of the Alton Ochsner Medical Foundation, New Orleans.

It was, therefore, logical that these agents be tried in patients with leukemia as well as those with malignant lymphomas. In acute leukemia the response to cortisone or ACTH has often been extremely dramatic. Striking remissions have been attained rapidly in a large percentage of such patients. However, unfortunately, the duration of these remissions has been all too short. In the vast majority of cases eight to twelve weeks is the maximum length of a remission. Somewhat less dramatic remissions have been seen occasionally in patients with chronic lymphatic leukemia. Of the malignant lymphomas a favorable response seems to have been obtained in Hodgkin's disease and reports indicate that at least in several cases it has been possible to attain a rather prolonged remission by repeating the course of therapy. To date, therapy with either cortisone or ACTH in other types of malignancy shows no promising results.

The field of cancer therapy which seems to be most amenable to hormonal agents is that of advanced cancer of the mammary gland in both sexes. This subject is now under extensive study in a large cooperative clinical investigation under the Research Committee of the American Medical Association, formerly the Therapeutic Trials Committee. It has been known for many years, in fact almost a century, that remissions can be obtained in young women with advanced mammary cancer by oophorectomy. As many as one third of the patients castrated have shown regression of lesions, sometimes lasting as long as two years. More recently, it has become apparent that castration is an even more efficacious therapeutic maneuver in males with cancer of the breast. Fifty per cent or more of patients so treated showed exceedingly dramatic regression of lesions.

One of the most interesting phases of endocrine therapy of cancer of the breast is that the age of the host plays an exceedingly important role in the response to hormonal agents. Of course, it is interesting to speculate whether the cancer which arises in an older woman is different from that arising in a younger woman, or whether it is the host itself in its effect upon the cancer that makes the difference. Nevertheless, the favorable response to massive estrogenic therapy is almost entirely confined to postmenopausal women. The longer the interval since the menopause the better the prognosis for regression following estrogen therapy. It does appear that as high as 50 per cent of women who have undergone the menopause five or more years before treatment will show objective regression of mammary cancer from estrogen therapy. At present there seems to be no reason for choosing one estrogen in preference to another. Both soft tissue and osseous lesions respond in this advanced age group.

In younger women, particularly of the premenopausal group, massive estrogen therapy may often lead to accelerations in growth of the tumor rather than regressions. Therefore, it would appear that estrogenic therapy should definitely be reserved for women who have undergone the menopause.

For younger women, the male sex hormone, the androgen testosterone, appears to offer some hope. Although the percentage response, that is, patients showing objective regression of the tumor, is less with testosterone therapy than with estrogens, it is nonetheless not inconsequential. Approximately 30 per cent of patients with advanced mammary cancer treated with testosterone in adequate dosage show objective regression of lesions for a varying length of time, probably not longer than one and a half to two years as a maximum. The results with testosterone are somewhat better for osseous metastases than for soft tissue lesions, but this question still must be settled by a study of large numbers of patients. Therapy with testosterone has additional advantages in that many of the patients experience tremendous subjective improvement even though the lesions may continue to progress. Most active researchers in this field have seen bedridden patients get up and go about their normal activities while there is objective evidence of continued expansion of the neoplastic lesion.

To many people the side effects of testosterone therapy are sufficiently distressing to preclude its use. Although difficult to understand, it is nonetheless true that many women are unwilling to trade a deep voice and facial hair for months of comfort and life. A search, therefore, has been carried out for agents which have the beneficial effects of testosterone without the androgenic effect. Certain reports in the literature, somewhat premature we feel, refer to methylandrostenediol, a synthetic compound related to testosterone. This compound has in our hands, also shown some evidence of production of regression in metastatic cancer of the breast. It is too early as yet to say how well the percentage response correlates with that obtained with testosterone, although it does appear that a greater percentage of patients do respond to testosterone therapy than to therapy with methylandrostenediol. However, it is even more apparent that this agent does not have the ability of testosterone to produce the feeling of well-being mentioned previously. Indeed, many of our patients treated with this agent have complained of excessive lassitude and weakness. As already mentioned, much additional work must be done for final evaluation of the role of this compound. It is my own opinion that it is inferior to testosterone with respect to the production of regression of the tumor, as well as to subjective feelings, and should take only second place to testosterone for therapy of advanced mammary cancer.

There is an increasing amount of work on the hormonal therapy of uterine and cervical malignancies. However, as yet insufficient data are available to warrant their discussion.

The excellent results obtained with endocrine therapy in cancer of the prostate are so well known to all of you that it will be mentioned only in passing. The recent report of a large joint series[2] would make it apparent that the combination of castration and estrogenic therapy yields the best long term results.

It thus appears that at least at present in its own restricted field, hormonal therapy does have something distinct to offer in neoplastic disease. Its sphere of usefulness may be expected to increase and we can hope that the future will bring greater promise.

REFERENCES

1. Dougherty, T. F. and White, A.: Influence of hormones on lymphoid tissue structure and function. Role of pituitary adrenotropic hormone in regulation of lymphocytes and other cellular elements of blood. Endrocrinology 35:1 (July) 1944.

2. Nesbit, R. M. and Baum, W. C.: Endocrine control of prostatic carcinoma. J. A. M. A. 143:1317 (Aug. 12) 1950.

TREATMENT OF CARCINOMA OF THE CERVIX AT CHARITY HOSPITAL

III. CUMULATIVE RESULTS AT THREE, FIVE AND TEN YEARS IN 1641 CASES.

MANUEL GARCIA, M. D.†

NEW ORLEANS

Results of the treatment of carcinoma of the uterine cervix at Charity Hospital have been reported to the Society on two previous occasions. Cases of the disease have continued to be referred in large volume, and bringing an appraisal of the results up to date may prove of interest. Hence this third report is submitted.

From April 1, 1938, to June 30, 1947, a total of 1641 authentic cases of carcinoma of the cervix were examined in the Department of Radiology. All had histologic confirmation; primary and recurrent lesions were included; and more than 99 per cent have been traced. The absolute survival rates observed are shown in Table 1. The

TABLE 1

CHARITY HOSPITAL OF LOUISIANA
PRIMARY AND RECURRENT CARCINOMA
OF THE CERVIX
RESULTS IN HISTOLOGICALLY VERIFIED CASES

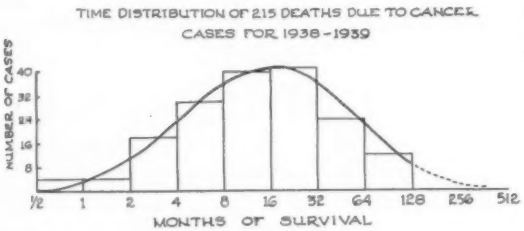
	3 YEARS	5 YEARS	10 YEARS
Period	1938-47	1938-44	1938-39
Cases Examined	1641	1159	286
No Treatment	70	60	11
Untraced	9	6	4
Survivors	674	347	67
Absolute Survival Rate	41%	30%	23%

†From the Department of Radiology, the Charity Hospital of Louisiana at New Orleans.

*Presented at meeting of the Orleans Parish Medical Society, October 9, 1950.

three year rates apply to the entire series, whereas the five and the ten year rates correspond to the period prior to 1945, and prior to 1940, respectively. The cumulative three and five year rates are about 3 per cent higher than in our previous reports, while the ten year rates are available for the first time.

Some idea of the ultimate meaning of the ten year results may be obtained from Fig. 1. It presents a histogram of the time



distribution of the 215 deaths due to cancer in the ten year series. By using logarithmic spacing for the time scale (number of months of survival) a fairly good approximation to a normal distribution is obtained with a good approach to symmetry about the median point at sixteen months. Since the period of observation corresponds to more than 90 per cent of the area of the normal distribution curve, it is reasonable to anticipate that few additional deaths will occur from reactivation of the neoplasm, even over the course of the next thirty years; or conversely, that all but a few of the 67 ten-year survivors are permanently cured of their cancer. Naturally, the surviving population will continue to decline, as other diseases take their toll.

The three year results obtained in cases seen prior to January 1, 1945, are contrasted in Table 2 with those obtained in more recent cases. The material is subdivided into stages according to the criteria of the 1937 revision of the League of Nations classification. Fourteen cases that had hysterectomy in addition to radiation therapy are included, but as shown in Table 3 this does not favor the end results.

TABLE 2

PRIMARY CARCINOMA OF THE CERVIX
IMPROVED RESULTS AT 3 YEARS

STAGE	I	II	III	IV	ALL
1938-44	116	306	501	150	1073
	79%	51%	30%	7%	39%
1947-47	53	92	275	36	456
	87%	77%	39%	8%	50%
BOTH	169	398	776	186	1529
	82%	57%	33%	8%	42%

TABLE 3

STAGES I AND II

	NO. OF CASES	3 YEAR SURVIVAL RATE
Complete Radiation	123	84%
Incomplete	7	43%
No Treatment	1	0%
All "Irradiated"	131	81%
Surgery and Radiation	14	79%
Total	145	81%

The group treated since 1945 manifests a substantial gain in the salvage. This cannot be attributed to better material, since advanced cases still make up 68 per cent of the total, and, with the exception of stage IV, there is an appreciable improvement in all stages, notably in stage II. As a matter of fact, the observed difference is statistically significant. It represents, therefore, not a haphazard fluctuation, but a real increment in the number of cases brought under control. Moreover, the sample is large enough to indicate that it will be maintained in the future if similar cases are similarly handled.

It becomes of interest then to determine the reasons that may account for the improvement. The question is not suitable for completely objective analysis, since there are a multitude of variables. But we would venture to find the explanation in the better facilities and organization for conducting the work, in better management of the patient before and during treatment, and in what we consider a better plan of irradiation.

As illustrations of the variety of factors that may have some influence on the change, the following may be mentioned: The radium supply was increased to 753 mg.; an additional 400 K. V. x-ray unit became available; a greater proportion of

patients were hospitalized by the creation of convalescent wards; penicillin and other antibiotics were provided freely; the blood bank was established; the nursing and technical staffs were enlarged; a more efficient follow-up service was set up, so that it became easier to persuade patients to return for completion of therapy after desertion; the number of residents was increased, and better coordination with the gynecological, urological, and surgical services was developed. As a consequence of the cumulative action of these and other factors it became possible to administer complete treatment in 82 per cent of the patients in the more recent series. With few exceptions full therapy was not possible in the remainder for medical reasons such as septic complications, distant metastases, uremia, uncontrollable hemorrhage, and ileus. Efforts to attain efficient organization and improved facilities thus may account for a share of the better results.

We are convinced, however, that the method of treatment overshadows in value all other factors. The plan of radiation employed has been previously described in all essentials. It possesses no unique features, but by precalculation of the x-ray and radium dosage we are assured that the quantity of radiation reaching the diseased area remains uniform in all cases, regardless of geometric variations, and at a predetermined range. Contrasted with the earlier period, the x-ray and the radium dosage in the recent series has been lower, the zone of tissue irradiated smaller, and the total period of treatment shorter. It appears that the choice of physical factors has been fortunate and that we are approaching optimum levels. The choice of dosage, however, was not made empirically, but was dictated primarily by an analysis of the cases managed by radiation in 1938-39 (already published), with the adjustments that have been required in the light of experience with cases subsequently treated.

The influence of the method of treatment can be very readily demonstrated: Among 10 cases that received no treatment there were no survivors; in 72 cases that had incomplete treatment the survival rate was 4 per cent; in 68 that had interruptions but completed treatment the rate was 38 per cent; and in 306 that received full treatment without complications the rate was 62 per cent. The results by stages in the last group were as follows:

Stage 1	47 cases	87%
Stage II	74 cases	82%
Stage III	181 cases	48%
Stage IV	4 cases	(50%)
Total	306	62%

It is thus apparent that whenever the impediments to full treatment can be overcome, the proportion of cases brought under control reaches rather satisfactory levels. In addition, a more detailed study of the response of various types of the disease, and of the influence of certain clinical factors, indicates that increasing salvage may be attained by a more careful adjustment of the radiation program to the features exhibited by the individual case. Consequently, it seems justifiable to repeat the statement made in our last report and now fully supported by the material under review. It was said then that the full possibilities of radiation therapy had not been achieved. We are still of the same mind, and hold the conviction that further progress is in sight.

SUMMARY

A third report on the results of the treatment of carcinoma of the cervix at the Charity Hospital of Louisiana based on 1641 cases is presented. The three, five, and ten year absolute survival rates are found to be 41, 30 and 23 per cent respectively. In 456 cases treated since January 1, 1945, the three year survival rate has risen to 50 per cent. Reasons that may account for the improvement are briefly discussed.

REFERENCES

1. Garcia, M. and Menville, L. J.: The treatment of carcinoma of the cervix at Charity Hospital. Preliminary report of end results. New Orleans M. & S. J. 96:87, 1943.

2. Garcia, M. and Schlosser, J. V.: The treatment of carcinoma of the cervix at Charity Hospital. II. Analysis of 716 cases. Three year and five year end results. New Orleans M. & S. J. 98:314, 1946.

3. Garcia, M. and Menville, L. J.: Surgical and radia-

tion therapy for carcinoma of the cervix. J.A.M.A. 137:1101, 1948.

4. Garcia, M.: Tissue dosage in the control of carcinoma of the cervix. Radiology 40:463, 1943.

THE INCIDENCE OF CARCINOMA OF THE CERVIX IN JEWISH WOMEN*

MAX SUGAR, M. D.†

AND

WALTER E. LEVY, M. D.**

NEW ORLEANS

INTRODUCTION

One[1] frequently encounters the idea expressed that carcinoma of the uterus is rare or unknown in Jewish women.

Boyd[2] states that uterine carcinoma is one of the commonest forms of malignancy; that it is more common in the cervix than in the body; and that uterine carcinoma is much less common in Jewesses than in any other race.

Vineberg[3] studied the cases of cervical carcinoma from 1893-1906 at the Mount Sinai Hospital of New York and found the incidence to be twenty times greater in non-Jews than in Jews. In a series studied at the same hospital by Rubin[4] from 1909-1918 the incidence was found to be seven and a half times greater in non-Jews than in Jews.

The cases at the Mayo Clinic from 1920-1925, studied by Horowitz[6] showed the incidence in Jews to be one sixth of that in non-Jews. Davidsohn[7], in studying a series of cases at the Chicago Mount Sinai Hospital from 1930-1938, found the incidence in Jews to be about one seventh of that in non-Jews. Treusch[8] studied the cases of carcinoma of the cervix at the Mayo Clinic from 1938-1942 and found 568 cases in non-Jewish women and none in Jewish women although the Jewish hospital population was between 7 and 8 per cent of the total.

MATERIAL

The above has prompted a review of the cases of carcinoma of the cervix at Touro Infirmary.

The cases in the period 1939-1949 were studied. The cases considered Jewish were those that were so designated on admission in answer to the question about religion. Only those cases in which the tissue had been diagnosed by the pathologist at Touro in that period were considered in this study as proven cases. Those that had been diagnosed elsewhere, or prior to 1939 at Touro, or clinically without tissue studies were considered clinical cases. In any instance where the diagnosis was questionable the slides were reviewed and discarded when equivocal.

There were in this eleven year period 159,292 total admissions of which there were 12,488 Jewish admissions.

By taking the total admissions to Touro in the first four months of this as a sample, it was found that of 5,439 admissions there were 61.9 per cent females and 38.01 per cent males admitted.

Assuming first, that Jewish women are readmitted with the same frequency as non-Jewish women and, secondly, that the ratio of males to females among the Jewish admissions is the same among the non-Jewish then it is found that the Jewish women made up 7.8 per cent of the female hospital population.

In the eleven year period there were 200 proven cases of carcinoma of the cervix at Touro; only one of these women did not specify any religion and this is omitted.

The expected number of cases in the Jewish women is 7.8 per cent of 199, that is 15.5. The actual number of cases was 5. The critical ratio of the expected to actual incidence is:

$$\frac{(0.078 \times 199) - 5}{\text{square root } (199 \times 0.9219 \times 0.0781)} = \frac{10.522}{3.785} = 2.7$$

There were 66 clinical cases, 4 of which were in Jewish women. By totaling the clinical and proven cases there were 265 cases; the expected number of cases in Jew-

*Read at the Medical Staff Meeting of Touro Infirmary May 10, 1950, New Orleans, Louisiana.

†Resident in Pathology, Touro Infirmary.

**Head of Department of Obstetrics, Touro Infirmary, Clinical Professor of Obstetrics of Louisiana State University Medical School, New Orleans, Louisiana.

ish women is 7.8 per cent of 265, that is 20.6, and there were 9. The critical ratio here is 2.67. This is very suggestive of a real difference existing in the incidence of carcinoma of the cervix in Jewish and non-Jewish women.

In this study, then, the number of cases in Jewish women at Touro Infirmary in the past eleven years is about one-third (at 37 per cent) of that expected. This would indicate an increasing incidence of carcinoma of the cervix in Jews compared with the findings in previous studies. Whether the increasing incidence is real or questionable cannot be evaluated, and if real the reason can only be guessed.

DISCUSSION

Some authors[1, 3] believe that there is an inherent immunity in the group to malignant affections of the genitalia, and this apparent immunity results from religious practices which over thousands of years have produced some sort of protection.

Vineberg[3] states that adherence to the Mosaic Laws of "Nidah, Tima and Tihara" may explain the relative immunity. According to these laws a woman shall count seven unclean days beginning with the first day of her period, and then seven clean days beginning with the day the flow ceases. Then the bath of immersion and purification is taken and marital relations may be resumed. If there is any flow after the seven unclean days then the count of seven clean days is begun again when the flow ceases. After delivery intercourse is prohibited for fourteen or twenty-one days depending on whether the child is a male or female respectively. The theory is that these restrictions prevent possible irritation to a congested, soft, boggy cervix and thereby the incidence of cancer of the cervix is reduced. Whether irritation is a factor in the production of cervical carcinoma will be discussed later.

These laws are not followed as such today because the religious practices are not adhered to by the vast majority. Indeed, these are common sense rules which are followed, more or less, by everyone; for example, present day obstetricians advise against marital relations in the last trimester and for about six weeks postpartum. If these practices should be factors influencing cervical malignancy, the incidence thereof should be decreasing in the population generally. As far as we know there have been no statistics to show this.

Another theory advanced in explanation is the practice of circumcision.[1] A recent study purported to show that a carcinogenic agent was present in human smegma[5] because it produced a skin cancer in a small number of rats. The number of cases was not significant; and because a cancer was produced in one species of animal does not prove that it does the same in another. Again the belief that carcinoma of the cervix can be caused by exposure to an unproven carcinogenic agent at infrequent intervals cannot be condoned.

The rarity of penile carcinoma in Jews is believed due to the absence of chronic irritation of the smegma and foreskin.[2, 7] Among Mohammedans, circumcision has been practiced at the age of 13 years, as long as it has been practiced among the Jews at the age of 8 days, and they have penile cancer as rarely as the Jews.[9] It would be interesting to compare valid incidence figures of carcinoma of the cervix in Jewish and Mohammedan women.

Furthermore, the practice of circumcision is now becoming almost universal and if it has any bearing on the incidence of carcinoma of the cervix it would be valuable to compare the incidence of carcinoma of the penis and cervix in the general population and in Jews several generations from now with present incidence figures.

Is there a protective factor in the genes of one family that has been transmitted? If there is, are the Chinese and African Jews considered members of this arbitrarily defined group; and what is the incidence of carcinoma of the cervix among them?

"For many years it has been assumed that chronic irritation of the cervix associated with erosions and lacerations is important as a cause of carcinoma, but increasing experience has failed to support this concept. The initial phases of carcinoma have not been found in the area of erosions or lacerations. In the cases of early carcinomas

which have been discovered, they do not appear to have originated from an area of inflammation.

"Multiparous women appear to have a higher incidence of carcinoma of the cervix than women who have had few or no children. This does not appear to be explained on the basis of lacerations of the cervix, as carcinoma of the cervix is found in as high a percentage of multiparous women who have had no lacerations; and, in those with lacerations the tumor is not found localized within the lacerated area. The high incidence of cancer of the cervix in multiparous women would appear to be related more probably, to the higher content of estrogenic hormones during pregnancy, as there is evidence that estrogenic substances have some carcinogenic activity. However, the high proportion of carcinomas of the cervix which occur after the menopause or castration seems to indicate that the sex hormones play no very important etiological role.

"The greatest degree of prolonged irritation of the cervix occurs in cases of uterine prolapse where there may be not only mechanical irritation of the projecting cervical tissue, but also thermic irritation due to exposure to the lower temperature of the air and chemical irritation by urine. However, the incidence of cancer of the cervix is not only relatively lower in cases of prolapse than in uteri in normal position, but actually the occurrence of carcinoma of the cervix is uncommon in cases of prolapse.[10]"

Adding up all the theories, there is no apparent reason for the existing difference in the incidence of cervical carcinoma in Jews and non-Jews.

SUMMARY

There is a common belief that carcinoma of the cervix is extremely rare in Jewish women.

In a series of 159,292 admissions to Touro Infirmary there were 265 cases of carcinoma of the cervix in the period 1939-1949; included in this group were 12,448 Jewish admissions with 9 cases of carcinoma of the cervix, which is approximately 37 per cent of the number of cases expected from a statistical standpoint. This is a higher incidence than in previous reports; the reasons for the difference in incidence between Jews and non-Jews and for the increased incidence found here cannot be accounted for.

REFERENCES

1. Queries and Minor Notes: J. A. M. A. 141:574, (October 22,) 1949.
2. Boyd, William: Textbook of Pathology; pp. 259-264, 647, 667-688, 4th Ed. 1943, Lea & Febiger, Philadelphia.
3. Vineberg, H. N.: Journal Mount Sinai Hospital of New York 10:33, 1943-44.
4. Rubin, I. C.: Quoted by Vineberg.
5. Plaut & Kohn-Speyer: Science, 165:391, 1947.
6. Horowitz, A: Surg., Gynec., & Obst., 44:355, 1927.
7. Davidsohn, I: Medical Leaves, 2:19, 1939, Medical Leaves Inc.: Chicago.
8. Treush et al: Am. J. Obst. & Gyn.: 52: 162, 1947.
9. Wolbarst: Quoted by Vineberg.
10. Anderson, W. A. D.: Pathology: pp. 1139, 1948: C. V. Mosby Company, St. Louis.

THE ROLE OF HORMONES IN THE MAINTENANCE OF PREGNANCY

JAMES W. HENDRICK, M. D.*

NEW ORLEANS

INTRODUCTION

Clinical and laboratory study of normal endocrine physiology has contributed significantly to our present knowledge of endocrine malfunction. The purpose of this paper is to correlate and interpret the present knowledge of hormonal actions and interactions with a view toward establishing rational bases for clinical and therapeutic application.

Emphasis has been placed on integration of all factors in the hormonal picture, and on the finely balanced physiology of the interacting endocrines. Following this line of reasoning, the first discussion is of the chemistry and general physiological actions of concerned hormones. The next portion of the paper deals with hormonal balances in a normal pregnancy, its inception and maintenance. The value of this discussion lies in the accepted fact that the abnormal can be wisely interpreted only in the light of the normal. The final division of the paper concerns abnormal conditions of pregnancy, treated with emphasis on demonstrable abnormal hormonal physiology, with a view toward arriving at a rational basis for therapy.

I. CHEMISTRY AND PHYSIOLOGY OF HORMONES OF REPRODUCTION

Chemically and physiologically the hormones concerned primarily with reproduction are divisable into two groups, i. e., the

*Thesis presented in 1949 Schering Award Contest and given honorable mention.

anterior pituitary group and the steroid group.

Pituitary Hormones—The pituitary gland occupies a key position in hormonal physiology. This paper is concerned mainly with its "sex" hormones liberated by the anterior lobe, but in keeping with the consideration of the endocrine interrelationships of the whole body, its other secretions deserve attention.

Extracts of the posterior pituitary gland have three distinct actions. They have an oxytocic action (stimulate the uterus), a pressor action (peripheral vasoconstriction) and an antidiuretic action (enhances tubular water reabsorption). There is no definite agreement as to whether this pharmacological activity is due to one substance or more. Two fractions have been separated[1]; one having predominantly pressor and antidiuretic action, termed "pitressin" and the other having mainly the effect on smooth muscle, termed "pitocin." However, Van Dyke[2] has recently isolated a pure protein which possesses pressor, oxytocic and antidiuretic activity, so perhaps this represents one hormone with a triple physiological effect.

The anterior lobe of the pituitary has been called the "master" gland since it secretes a number of "trophic" hormones which stimulate, regulate, and maintain the structure of other endocrine glands of the body.

Among these principles are gonadotropins, growth hormone, thyrotropin, adrenocorticotropin and prolactin. Extracts relatively free from other actions have been produced for each of these principles. Other effects of anterior pituitary extracts are ketogenic, insulin-antagonizing or glycotropic, diabetogenic, parathyrotropic and pancreatropic. These actions have not been demonstrated in separate fractions.

As in the case of the posterior pituitary, it hardly seems likely that each of these physiological effects represents a distinct entity. It has been suggested that each of the different products obtained in nearly pure form represent "hormone fragments."[3] Histologically, of the three characteristic cells of the anterior lobe, only the acidophils and basophils have been shown to elaborate physiologically active principles.[4] This, however, does not limit the possible number of hormones because there is no evidence that the complex activities of a cell may not elaborate more than one chemical secretion.

Prolactin was the first anterior pituitary hormone isolated and crystallized free from other anterior lobe constituents.[5] It is a protein, destroyed by tryptic digestion. Its influence upon the mammary gland is to stimulate normal lactation following parturition, after the breasts have been properly developed by the two ovarian hormones.

In 1934 Collip and Anderson[6] noted that rats after repeated injections with the thyrotropic principle became refractory, eventually failing to respond to large doses. Injection of this rat's serum into other animals resulted in antagonizing the thyrotropic activity in the recipient animal. This antagonistic substance was called *antihormone*. Controversy has arisen as to this term, other workers believing that the substance may be an immune body developed to the protein hormone. A great deal of investigation is being conducted in this field, including parabiosis experiments. The further development of this subject may possibly offer a therapeutic approach to endocrine hyperfunction by the use of antihormones.

Pituitary Gonadotropins:—The gonad-stimulating principles or gonadotropins are protein in nature but otherwise little is known of their chemical properties. No one member has been isolated or synthesized and there has been some disagreement as to the individuality of the principles. Recent fractionation and purification procedures,[8,9] however, have accumulated evidence in favor of the existence of two distinct hormones. One of these elements is the follicle-stimulating hormone, (FSH), whose primary effect in the female is to stimulate growth and maturation of the ovarian follicle and estrogen production, and, in the male, to stimulate spermatogenesis. It is identical

with the gonadotropic substance found in the urine of castrate and menopausal women, in the urine of castrate animals and men, and in the urine of pregnant mares.[4]

The other principle is the luteinizing hormone, (LH), which brings about luteinization of the ruptured follicle and progesterone production in the female, and in the male stimulates the interstitial cells of the testis to produce male sex hormone. A substance with very similar action, chorionic gonadotropin, has been obtained from the urine of pregnant women and is the basis of the Ascheim-Zondek pregnancy test and modifications. Its origin, however, is from the chorionic epithelium of the placenta, and it must be regarded as distinct from the hypophyseal gonadotropes.[10]

The blood serum of pregnant mares is another source of gonadotropic material, (PMS).[11] PMS has many properties common to the pituitary gonadotropes, but appears to be an entirely new entity. One peculiar characteristic is its nonexcretability, i.e., even with a peak blood level, none appears in the urine.[12]

The two factors FSH and LH, when combined in a definite quantitative proportion, act synergistically to produce follicular rupture.[13, 14] Ovulation is not caused by either principle alone.

It bears emphasis that the relationship between the gonadotropic hormones and the gonads, like all other endocrine relations in the body, is not a one sided affair. As demonstrated by parabiotic experiments, the gonads normally exert a restraining influence on gonadotropic functions of the pituitary.

Another example of this interrelationship of hormones was demonstrated by Fevold[15] who showed that both FSH and LH are concerned with estrogen production. The amount of LH necessary for this complementary effect is very small, 0.0008 mg. causing 90 per cent increase in uterine weight when added to an amount of FSH which alone would have no effect on the uterus.

Steroid Hormones: The steroid group of naturally occurring sex hormones includes the estrogens, progesterone and androgens. The basic chemical structure of these steroids is similar in that they all possess the cyclopentenophenanthrene nucleus.[16] This same steroid nucleus occurs in bile acids, cardiac glycosides, vitamin D, cholesterol, and the hormones of the adrenal cortex.

Estrogens: The estrogenic hormone is responsible for the development of the sex organs and secondary sex characteristics at puberty and their maintenance and function during adult life. For a hormone to be considered estrogenic it must produce, in a castrate animal, the changes resulting from ovarian follicle activity, i.e., growth of the genital tract epithelium and myometrium and development of the duct system of the breast.

The first crystalline estrogen was isolated from pregnancy urine by Doisy and co-workers, also by Butenandt, in 1929. This was estrone; later estriol was isolated. Estradiol, now known to be the primary hormone of the ovarian follicle, was obtained by reduction of estrone, even before it was extracted from follicular fluid. Alpha-estradiol has approximately twelve times the activity of estrone and is at least eighty times more potent than estriol.[17] The clinical use of the estrogens has been advanced by the finding that esters of these compounds have a more prolonged activity. A number of synthetic compounds with estrogenic activity have been prepared, the most important of which is diethylstilbestrol, characterized particularly by the effectiveness of its oral therapy. It does not have a sterol nucleus but Dodds[18] has pointed out that its structural formula is quite similar.

The metabolism of the estrogens has received a great deal of attention, for as will be shown later, it is intimately associated with the hormonal physiology of pregnancy. There is now general agreement that the liver is the major site of rapid inactivation for the estrogens,[19, 20] though there is some evidence of there being an enterohepatic circulation.[21] Progesterone is important in that it inhibits the excessive destruction of

alpha-estradiol and facilitates the conversion of estrone to estriol.[20, 22] Thus in the luteal phase of the menstrual cycle and in pregnancy, where progesterone secretion is maximal, estriol is the principal estrogen excreted.

Urinary excretion products are in the form of estrone and estriol glycuronates, though less than 10 per cent of administered estrogens can be recovered in the urine, possibly due to its enterohepatic circulation. These conjugated forms, which can be freed by acid hydrolysis, have little or no physiological action.

In human pregnancy serum estrogen is present chiefly in the free state, but as much as 23 to 50 per cent is in a combined form, evidently bound to serum proteins since protein-free filtrates of the serum have no estrogenic content.[23, 24] In late pregnancy urine over 99 per cent of estrogen is in a combined form, largely estriol glycuronidate. Shortly before parturition there is a considerable increase in free estriol in the urine, as the combined forms begin to decrease.[25]

Progesterone: The primary hormone of the corpus luteum, the steroid progesterone was first demonstrated by Corner and Allen.[26] Secreted in sequence with the follicular hormone under the influence of the rhythmic stimulation of the anterior pituitary, the influence of the two hormones on the uterine endometrium accounts for the menstrual cycle. The luteal hormone is necessary, as we shall see later, in the preparation and maintenance of the uterine endometrium for the normal implantation and nourishment of the embryo. It has an inhibitory effect on the uterine musculature, keeping the pregnant uterus in a quiescent state. It suppresses further ovulation during pregnancy, stimulates proliferation of the lobule-alveolar system of the estrogen-developed breast and, as previously mentioned, has a significant influence on estrogen metabolism.

Progesterone has been synthesized from a soy bean sterol, isolated in crystalline form, and also produced by conversion from its urinary excretion product, pregnandiol, which is the major end product of progesterone metabolism.[27] Like urinary estrogen, it is present in the urine chiefly in a combined form, as a mono-sodium salt of pregnandiol glucuronic acid.[28] Determinations are usually made by gravimetric methods, but a colorimetric method has been described by Guterman, which is of value in the rapid diagnosis of pregnancy.[29] It has been shown that the excretion rate of pregnandiol glucuronidate can be considered an index of progesterone production in the body.[20, 30, 31]

It is the coordinated interplay of the pituitary gonadotropins, estrogen and progesterone, which produces the female menstrual cycle, its phases being mirrored in the uterine endometrium. As the level of the gonadotropins in blood and urine slowly rises from traces in the first week to their maximum of 30 or more mouse-uterine weight units at the midcycle,[32] the maturation of the ovarian follicle progresses. As emphasized previously, FSH, though dominant in this period, is not acting alone, but is complemented by LH in stimulating the maturing follicle to produce estrogen. The endometrial mirror reflects this estrogenic influence by entering its proliferative phase. As the estrogenic activity reaches its midcycle peak, a proper synergistic mixture of FSH and LH occurs and ovulation is produced.

Following ovulation the luteinizing hormone decreases less rapidly than FSH, and its predominance results in formation of the corpus luteum. This new endocrine gland elaborates progesterone under whose influence the proliferative endometrium enters its progestational phase, capable of receiving and maintaining a fertilized ovum. The corpus luteum also secretes estrogen, which has a secondary peak in the premenstrual phase, four or five days preceding the flow.

If conception has not occurred, gonadotropic activity diminishes with accompanying corpus luteum degeneration; both estrogen and progesterone fall to very low amounts, and menstruation follows.

II. HORMONAL PHYSIOLOGY OF NORMAL PREGNANCY

The role of endocrines in the physiology of pregnancy has been the object of a tremendous amount of study, both experimental and clinical. Without losing sight of the influences of the nervous system, metabolic activities, and other bodily physiology, it is now generally agreed that reproduction—from fertilization of the ova to birth of the child—is dependent upon the balancing and counterbalancing actions of the whole endocrine system.

Every female sexual cycle anticipates fertilization of the ovum. Therefore, the object of the proper gonadotropin-estrogen-progesterone balance is the preparation of the endometrium for reception and nourishment of the fertilized egg. I interpret this progestational endometrium as representing the climax of the female sexual cycle—menstruation being aptly described as the "weeping of a disappointed uterus". When fertilization takes place, however, loss of the endometrium is averted—progestational changes advance to decidua formation and pregnancy progresses. What has caused this change of course? The answer entails consideration of the hormonology of pregnancy.

Endocrine Assays In Pregnancy: During the past decade a host of methods have been evolved to demonstrate the presence of various hormones in the body fluids. Correlation of these findings with the clinical picture has resulted in a clearer understanding of normal and abnormal endocrine physiology and given a rational basis for the etiology, diagnosis, and therapy of various dysfunctions.

Gonadotropic Hormones In Pregnancy: Recent work[33] indicates that the luteotropic agent responsible for the early development of the corpus luteum of pregnancy is chorionic gonadotropin (CG).

After ovulation in the sexual cycle has occurred, the normal corpus luteum maintains its function for twelve to fourteen days. The fertilized ovum requires eight to ten days for its migration down the tube and its implantation in the endometrium. Following the line of reasoning that a new luteotropic agent is necessary to prolong the functional life of the corpus luteum, we would expect such an agent to make its appearance at this time—just as the chorionic villi make contact with the maternal circulation, and just as the corpus luteum would otherwise begin to degenerate. Such is the case. The presence of gonadotropin in blood and urine may be demonstrated as early as ten to thirteen days after ovulation.[34, 36]

It is generally agreed that most of the pregnancy gonadotropes are derived from the chorionic epithelium of the placenta. This is suggested by the fact, as mentioned previously, that placental and hypophyseal gonadotropes differ biologically.[10] Another argument in favor of their placental origin is that gonadotropes have been produced in vitro by placental culture tissues.[36] As to the functional activity of the anterior pituitary in pregnancy there appears to be some controversy. Although it is well established that the gland contains little or no gonadotropic hormone during pregnancy[37] some interpret this as indicating diminished activity, and others believe it due to rapid discharge of its products.[38]

From the time of its first appearance ten to thirteen days after ovulation, the level of CG in pregnancy blood and urine rises rapidly.[34] By the time of the second missed period, a peak of the curve is usually

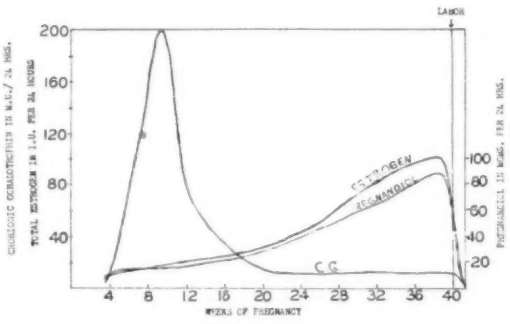


Figure 1

reached.[39, 40] This high level is maintained for only a comparatively short time, one to three weeks, during which period average values commonly reach 10,000 mouse-uterine weight units per 100 cc. of blood,

with a transient peak up to 30,000 M.U.[16] In the urine the twenty-four hour values are about ten times as much. A rapid fall from this high level is the next occurrence, so that about the fourth month of gestation a rather constant low level is reached with serum values approximately 100 M.U. per 100 cc. During the last month or two of gestation there is frequently a slight secondary rise in values. At parturition, gonodotropins fall rapidly, and reach nonpregnant levels within a week.

In connection with this curve of chorionic gonadotropin values it has recently been shown experimentally that the injection of CG in the luteal phase of the menstrual cycle would prolong the functional life of the corpus luteum, increase the output of pregnandiol, and delay menstruation.[33] This work gives an insight to the role of CG in human pregnancy. It has also been noted that after a varying time, the same dosage of CG failed to maintain the corpus luteum, and required increasing amounts to maintain its function as it grew older.[34] On the basis of the rapidily increasing amounts of CG formed in early pregnancy, this correlation appears significant.

To be considered later is the relationship of increased quantities of CG to late pregnancy accidents.

Steroid Hormones in Pregnancy: Discussion of the steroid hormones of pregnancy will first involve a consideration of their sources. As shown previously, when fertilization takes place in the human sexual cycle, the corpus luteum, instead of degenerating and withdrawing its hormones, is maintained by CG and continues to secrete its principles in physiologic balance.

The story of the progression of our knowledge concerning the corpus luteum is so interesting and informative, especially as related by Corner,[41] that it will be of value to review it here.

Evidently the embryologist, Born, of Sweden first conceived the idea that the corpus luteum was an organ of internal secretion and concerned with the protection of the early embryo. Just before his death he imparted his hypothesis to one of his students, Ludwig Fraenkel, whose task it became to test the theory by animal experimentation. The work of Fraenkel is now well known, for he found that when the corpora lutea of a pregnant rabbit were excised, no pregnancy ensued—that the implantation of the embryo depends upon the corpus luteum.

At about the same time (1903-1910), two French histologists, Ancel and Bouin, found that in early pregnancy the lining of the uterus undergoes remarkable change, which we now term progestational proliferation, i.e., "growth and change which favors gestation". To relate the cause of this change to the corpus luteum, these men devised the plan of mating their female rabbits to males rendered infertile by the tying off of their seminal ducts. These females ovulated and formed corpus lutea, but did not become pregnant, thus differing from controls only in that their ovaries contained corpus lutea. Examination of their uteri showed typical progestational proliferation, indicating that the functional state of the uterus depends upon this gland.

Another classical experiment was conducted by Corner in 1929,[41] who found that if the corpora lutea of pregnant rabbits were excised fourteen to eighteen hours after mating, the embryos died on the fourth day, as soon as they entered the uterus. In the absence of progestational proliferation, the fetal bed was unprepared to receive the embryo.

Thus by early experiments such as these it became apparent that the corpus luteum was vitally concerned in the maintenance of pregnancy by its creation of conditions in the uterine mucosa which are essential for the nidation and retention of the developing ovum.

Considerable debate has centered around the question as to the length of time the corpus luteum is necessary during human pregnancy. From experiments, such as cited above and other work, we know that in smaller mammals such as the rat, mouse, and rabbit, it remains indispensable up to term. In the human, however, the results following bilateral oophorectomy in preg-

nancy show that it is necessary only during the first trimester. In some cases the corpus luteum can be removed even earlier than this without interruption. Ask-Upmark[42] collected data on 51 cases which had the corpus luteum removed during the first two months, with only 17 abortions occurring in the group. Pratt[43] reports a corpus luteum removed on the twentieth day, and the patient continued through a normal pregnancy. Moreover, many workers, including Venning and Browne,[31] on the basis of studies of pregnandiol excretion following oophorectomy, have concluded that the placenta takes over the chief burden of steroid hormone production from the corpus luteum, usually from the late second to third month of pregnancy.

During the early weeks of gestation, estrogen and progesterone levels of blood and urine rise very slowly, the level of excretion being about the same as the maximum reached during the luteal phase of the normal menstrual cycle. It is not until about the eightieth day that the values of these two substances rise over this nonpregnant level.[44] This period, varying from the seventieth to ninetieth day of gestation, has been called the "critical" period, for it is at this time that the transfer of function from the corpus luteum to the placenta takes place. Throughout the remainder of pregnancy, the two curves are roughly parallel, both reaching a maximum about a week prior to the onset of labor. At this peak, the excretion of urinary pregnandiol is approximately 90 mg. per twenty-four hours, and urinary estriol reaches 25 to 40 mg. per 24 hours. From this level they progressively decrease to values of 60 and 11 mg. per twenty-four hours, respectively, at the onset of labor.[22]

Integration of the Hormones of Pregnancy: We have seen that the physiology of pregnancy is such that a new endocrine gland, the placenta, is formed to insure adequate and balanced secretion of estrogen and progesterone during pregnancy. It logically follows that these two principles must play an important role in the maintenance of pregnancy. The influence of the corpus luteum on the endometrium has already been discussed. This action is primarily due to progesterone, but proper amounts of estrogen are necessary to "prime" the uterus so that this progestational proliferation can be produced.

Considerable study has been undertaken to determine the influence of the two hormones upon the physiology of the breast. During gestation, on the basis of histologic alterations, the mammae have a proliferative phase, which extends through the first half to two-thirds of pregnancy, and a secretory phase, which becomes more marked as term approaches. In the proliferative phase, estrogen induces duct growth, and progesterone stimulates proliferation of the lobule-alveolar system previously developed by estrogen.[45] The secretory phase depends upon the action of the anterior pituitary lactogenic hormone on the breast previously primed by estrogen and progesterone.[12] Apparently, the high titer of estrogens during pregnancy inhibits true lacatation, which then occurs in the postpartum period as estrogens rapidly diminish. This whole subject of breast physiology is, however, exceedingly complex and unsettled at the present time, though undoubtedly hormonal control plus nervous impulses are the influencing factors.

Coordination of endocrine factors also produces structural modifications in the generative tract during pregnancy. The general growth-promoting effect of estrogen on the uterus is exerted by augmentation of blood flow through the tissues, and progesterone causes waves of cell division in the muscle.[41] Other influences consist of increased vascularity of tissues, mucification of the vagina, and a thickening, softening and loosening of tissues about the pelvic joints. Hisaw[46] (1926) has demonstrated that the relaxation of the pubic joints in the guinea pig is due to a specific substance which he named "relaxin". These identical pelvic modifications have not been observed in the gravid woman, but Zarrow[47] (1947) has found "relaxin" in human pregnancy blood.

That there is a balanced thyroid-gonadal

interrelationship in pregnancy is suggested by the transient thyroid enlargement which occurs. This hyperactivity, with a 20 to 30 per cent rise in basal metabolic rate, is generally interpreted to be a part of the acceleration of endocrine activity designed to meet the demands of pregnancy; possibly, this increase represents the sum of fetal and maternal metabolism. Chu[48] has shown that thyroidectomy in pregnant rabbits caused resorption or abortion of the embryos, and by administering dessicated thyroid he was able to produce normal litters from thyroidectomized rabbits. Thyroid-gonadal association in humans is also emphasized by the fact that reproductive disorders are apt to occur in thyroid disease and often benefitted by thyroid therapy.

It has been well established that hormonal stimuli exert considerable influence on myometrial activity but the exact action of each hormone has been difficult to define. It must be emphasized that normal balance is of greater significance than quantitative production, and that a predominance of either hormone may upset the balance needed to maintain uterine quiescence.

Studies on the mature nonpregnant human uterus by the intrauterine bag method and by bimanual palpation indicate that during the period of follicular activity the movements of the uterus are rhythmic, frequent, of small amplitude and high tonus.[12] The same type of activity is seen when estrogen is administered to the human castrate. Concerning progesterone it is agreed that in nonpregnant uteri of both lower mammals and humans its presence is associated with large, slow movements and loss of tonus. Studies of the myometrial reactivity to oxytocin yield varying results, in accord only that the sensitivity is greatest just before and during the menstrual flow.

By the use of external hysterography, spontaneous contractions of the gravid human uterus have been noted to commence near the one hundred and sixtieth day and increase progressively thereafter, with the approach of term marked by increasing tension.[49] Since this increase in motility coincides with the rise of the estrogen level in blood and urine during gestation, it has been suggested that estrogen is the myometrial stimulator. Experiments to prove this action on the pregnant uterus, however, have been equivocal; in fact, Heckel and Allen[50] postponed parturition in experimental animals by estrogen injection shortly before term. Recently, also, massive does of estrogen and stilbestrol have been administered to pregnant women without causing premature labor or other change in the course of pregnancy.[51]

The role of progesterone in the maintenance of pregnancy became quite evident when Corner[41] demonstrated that progesterone prevented the abortion which would otherwise follow ovariectomy in the pregnant rabbit. Postponement of parturition can also be produced by progesterone administration.

The literature is replete with reports, pro and con, on the effects of each of the steroids on the pregnant uterus. In vivo, however, the effects are not due to the influence of a particular hormone, but are dependent on a combination of principles so regulated by bodily physiology that the gravid uterus is maintained quiescent.

Though an altered hormonal environment is certainly one of the most important factors in parturition, the actual initiation of labor cannot be ascribed to any one influence. Certainly the placenta plays a role in the chain of events, probably through aging or degenerating processes; characteristic degenerative morphological changes are demonstrable in term placentas.[52] The increasing uterine distention at term is thought to contribute to myometrial irritability; certainly local factors play a part, for when two pregnant animals are joined in parabiosis, labor in one does not cause contractions in the other. Nervous connections of the uterus undoubtedly participate, since premature labor can be precipitated by emotional states. All these factors plus others have their part and, balanced with one another, are all involved in the onset of labor.

One of the older hypotheses concerning the role of endocrines in labor is based upon

the rising estrogen level of blood and urine as term approaches, with increase in the free forms at expense of the combined forms. This free estrogen is believed to sensitize the uterus, possibly to the oxytocic principle of the posterior pituitary, thereby initiating labor.

A newer concept in the hormonal physiology of labor has been made possible by more perfect technics to determine hormone excretion and by further investigation of estrogen and progesterone metabolism. These recent findings emphasize the role of withdrawal of hormone support from the uterus at term and demonstrate the similarity of the basic mechanisms of menstruation, premature deliveries and labor. Most important of all, the indications are that these concepts will have clinical applications creating new opportunities for fetal salvage.

Lyon[27] (1946) maintains that labor occurs due to a progesterone deficiency. Using a titrimetric determination rather than the original gravimetric method of Venning and Brown he assayed late pregnancy urines for sodium pregnandiol glucuronidate, and was able to demonstrate a pronounced fall in pregnandiol excretion during the last several days preceding the inset of term, premature and postmature labor.

Smith and his co-workers at the Fearing Research Laboratory have contributed a great deal to the present knowledge of estrogen-progesterone metabolism. In the course of their work they have arrived at the conclusion that hormonal withdrawal is the common denominator of menstruation, term labor, premature delivery, some stillbirths, preeclampsia, and eclampsia. Their findings will be discussed fully in connection with estrogen-progesterone metabolism and accidents of pregnancy.

Estrogen-Progesterone Metabolism in Pregnancy: This paper has stressed the functional interrelationships of the endocrine glands. Recent work in endocrinology has indicated that these relationships, especially estrogen-progesterone metabolism, are of prime importance in the physiology of pregnancy.

The first observation (1931) concerning the influence of progesterone on estrogen excretion was that the amount of injected estrogen recoverable in the urine was considerably more when accompanied by progesterone than when estrogen was given alone.[53] Along this same line of investigation, Pincus[54] was able to show that rabbits with active corpus lutea excreted four times as much estriol in the urine as did rabbits without active corpora lutea—and found that he could equalize the estrogen excretion by administering progesterone to the latter group.

The fundamental aspects of estrogen-progesterone metabolism are two in number: (1) Estradiol conversion to estrone is a reversible reaction, the rate and direction being dependent (by the law of mass action) on the irreversible estrone to estriol conversion.[20, 55] (2) Progesterone facilitates this conversion of estrone to estriol, thus depressing their rate of inactivation or destruction.[56, 20, 22]

The applicability of these two principles may be seen by noting hormonal levels at the thirty-eighth week of pregnancy. At this time there is a maximum production of progesterone, as measured by the peak of pregnandiol excretion, maximum estriol excretion, indicating maximum conversion of estrone to estriol, and the lowest percentage of activity due to estradiol. Following this peak period, the drop in urinary estriol and pregnandiol, accompanied by an increasing percentage of activity due to estradiol, implies decreasing production of progesterone, with accompanying decreased rate of conversion. It should be emphasized that during this time, as well as in all phases of normal pregnancy, estriol and pregnandiol excretion are found to exactly parallel each other.[22] This aligns with the basic premise, i.e., progesterone enhances conversion of the estrogens to estriol.

Since the rate of estrogen destruction as opposed to its metabolic conversion plays an obviously important role in this metabolic scheme, the Smiths devised a pro-

cedure for evaluating the amount of estrogen-breakdown products in the urine. This consisted in performing both a Zn-HCl hydrolysis (Tzn) of pregnancy urine and the usual HCl hydrolysis (To). An increase in the yield of estrogenic potency of Tzn over To is a constant finding, indicating a rehydrogenation of oxidized estrogen breakdown products back to material with estrogenic activity, and providing a relative index of estrogen destruction in the body. Convincing evidence supporting this conclusion is that administration of estrone causes an increase in the "unaccounted for" Tzn activity amounting to 10 to 60 per cent of the estrogen given.[57] The applicability of this Tzn:To ratio is indicated by the fact that its highest value has been found at times, in both normal and pathological processes, when there is a decreased excretion of pregnandiol, a decreased excretion of estriol, and an increased percentage

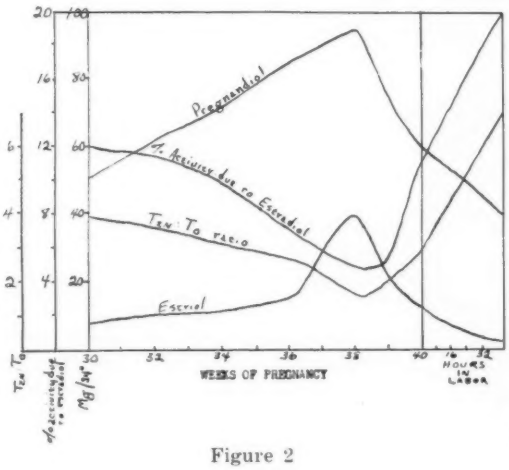


Figure 2

of activity due to estradiol—signifying that destruction of estrogens rather than metabolic conversion is occurring. Its value is lowest at the thirty-eighth week of pregnancy when, as we have seen, there is a maximum production of progesterone and a maximum rate of estradiol to estrone to estriol conversion.

The fact that this rate of estrogen inactivation bears a constant inverse relationship to the urinary excretion of steroid hormones leads to an interesting and therapeutically applicable concept. We have seen previously than when steroid output decreases, Tzn:To rises. In normal pregnancy this pertains at around the sixteenth, twenty-eighth, and thirty-sixth weeks, and following each rise in the Tzn:To curve there is a period of rapid increase in the urinary excretion of estrogens and pregnandiol. A logical interpretation of these relationships is that the oxidation products of the estrogens are involved in the stimulation of ovarian or placental steroid secretion. This concept, first reached by biological observations, is strengthened by the fact that a known degradation product of estrogen, Westerfeld's lactone, has been shown to stimulate release of gonadotropic factors from the anterior pituitary,[57] and to possess about the same estrogenic activity as beta-estradiol.[58] Investigation of related aspects of estrogen degradation products is high on the agenda of many research workers at the present time.[59]

On this basis, the continued secretion of estrogen and progesterone in pregnancy is dependent upon the oxidation products of the estrogens. As levels of progesterone and estrogen rise there is more conversion and less destruction of estrogens; subsequently, there is decreased placental steroid stimulation, resulting in increased oxidative inactivation, which in turn brings about increased production of the placental steroids.

Thus about the thirty-eighth week of pregnancy the production of estrogen and progesterone is at such a high and balanced level that there is a maximal peak of conversion and a minimum level of destruction. At this time with nervous stimuli, aging of the placenta, uterine distention, and other factors playing a part, the lack of stimulation for steroid secretion results in withdrawal of hormonal support and parturition occurs.

As I have intimated previously, this concept is receiving a great deal of attention at the present time, and obviously it will require even more substantiation before it is universally accepted. I believe, however, that much of the value of this concept lies

in the fact that it establishes hormonal withdrawal as the common denominator of both normal and abnormal delivery, enabling the physician, as we shall see later, to approach the therapeutics of pregnancy accidents on a rational basis.

III. HORMONAL PHYSIOLOGY IN ABNORMAL CONDITIONS OF PREGNANCY

In endocrinology, as in all other phases of biologic phenomena, the abnormal can be wisely interpreted only in the light of the normal. On this basis, the two previous sections of this paper have been at attempt to integrate and interpret the present pertinent knowledge concerning hormonal actions and interactions in both the human sexual cycle and pregnancy. This last part of the paper will serve to correlate this knowledge of normal mechanisms with the findings in abnormal conditions, with the view ever in mind of establishing rational bases for therapeutic application.

Our primary interest lies in fetal salvage, for fetal deaths certainly constitute the greatest wastage of potential human resources. Whether the factor or factors involved in fetal mortality operate before or after conception, early or late in pregnancy, does not restrict the application of knowledge of the normal physiology in a corresponding period. Reviewing previous observations of normal reproductive physiology, it is apparent that there are several prerequisites for a successful pregnancy.

(1) The fetal bed, stimulated by estrogen and progesterone, must undergo progestational proliferation, thus being properly prepared for reception and nidation of the embryo.

(2) The fertilized ovum must be normal to insure its continued viability.

(3) The corpus luteum of pregnancy and the placenta, in turn, must maintain a constant, adequate and balanced level of estrogen, progesterone and gonadotropic hormones.

(4) The uterus must adapt itself to accommodate the growing embryo, and the myometrium must be maintained in a quiescent state.

These considerations provide an insight into the number and complexity of factors involved in expulsion of a previable fetus, but at the same time stress the necessity for normal endocrine relationships. Proper understanding of the various etiologies of abortion is necessary to evaluate the probable role of endocrinopathy.

Fetal faults such as defects in either gamete, incompatibility of the germ cells, or abnormality of the fetal trophoblast are considered to be possible causes of spontaneous abortion. Maternal faults may also be responsible, such as diseases and abnormalities of the decidua, unfavorable hormonal environment, systemic diseases, nutritional deficiencies, trauma, psychic factors, and heterologous blood groups. The relative importance of the heredity and environment in intrauterine life has been a subject of much controvery. It has been well established by workers such as Hertig[60] and Mall[61] that from 50 to 80 per cent of early abortuses are pathologic. The matter of vital importance, however, and the subject of controversy is (1) whether abnormalities of the germ cells themselves or (2) abnormalities in the maternal developmental environment account for the pathologic abortuses. Mall held the latter view, stating that a defective maternal environment, usually in the nature of faulty implantation, is the chief source of abnormality.

Hertig[62] (1944) made pathological examinations of 1000 abortuses and came to the conclusion that one-third of all spontaneous abortions contain a normal living fetus at the time the patient is first seen. A greater percentage than this is theoretically salvageable by the application of early preventive and prophylactic therapy designed to physiologically better the maternal hormonal environment, especially in women who have aborted in a previous pregnancy.

This concept is supported by previous observations in this paper: (1) The work of Fraenkel showed that progestational proliferation, produced by balanced hormonal influences, is necessary for implantation of

the embryo. (2) Corner showed that in the absence of corpora lutea, the embryos became nonviable on entering the uterus. (3) After implantation, uterine quiescence is maintained by the proper hormonal balance. (4) The vascularizing and growth-promoting effects of hormones are necessary to develop the uterus so that it may accommodate the growing fetus. (5) The removal of the corpus luteum at any stage of the pregnancy in smaller mammals and before the second or third month in humans results in abortion. (6) The time at which most abortions occur, about the third month, corresponds to the "critical period," which marks the transfer of hormone production from the corpus luteum to the placenta. (7) Proper thyroid-gonadal relationship is necessary, as shown by animal experimentation and clinical observation.

The next logical step is to examine each of the abnormal conditions in pregnancy which cause expulsion of previable embryos to ascertain if any constant abnormal hormonal patterns are present.

Spontaneous and Habitual Abortion: The incidence of noninduced abortion is such that approximately 250,000 to 300,000 occur each year in this country,[63, 64] representing 10 to 13 per cent of all pregnancies. This frequency is also reflected in the maternal mortality rate, the deaths from abortion constituting 30 to 35 per cent of maternal deaths from all causes.[65] The difficulties encountered in estimating the prevalence of spontaneous abortion is apparent, for many fail to come to the attention of physicians, or occur so early as to be considered irregularities of menstrual flow.

With recent advances in reproductive physiology, such as this paper has reviewed, it is now possible to determine the presence of hormonal abnormalities and arrive at logical therapeutic approaches.

It has long been recognized that spontaneous abortions tend to occur more commonly in the late second and third months. In a series of 500 cases of abortion the average time of onset of symptoms was found to be the eighty-first day from the beginning of the last menstrual period.[34] According to Hudgins[66] over 75 per cent of abortions occur during the second and third month. By determination of pregnandiol excretion, as noted previously, it has been concluded that this is the "critical period" in which transfer of function from the corpus luteum to the placenta takes place. Thus, it is apparent that deficiency of hormonal principles at this time may be due to the corpus luteum waning too soon or to retardation of placental production. Browne,[34] on the basis of pregnandiol determinations in normal pregnancy and spontaneous abortion, has found that progesterone production is at a low ebb during this period, and begins to rise between the seventieth and ninetieth day, marking the assumption of placental function. He recommends the administration of progesterone, 5 mg. daily, beginning before the time of onset of symptoms at the critical period.

Precise clinical evaluation of the results of progesterone therapy in spontaneous abortion is difficult. One factor is that other therapy is often employed, such as bed rest, sedation, vitamin E, and thyroid administration. Another difficulty lies in the fact that it cannot be determined which threatened abortions will go on to term regardless of treatment and which would result in actual abortion. Hertig's review of the subject, however, concluded that approximately 60 per cent of threatened abortions abort if untreated.[62] A general assessment of the value of hormonal therapy has been made by Taussig: "No method of treatment for the prevention of abortion has been attended with as much success as that of endocrine therapy.[64]

Mason[67] (1945) concludes that progesterone is valuable in the treatment of abortion from the results of a series consisting of 34 threatened abortions, manifested by painful contractions and bleeding, of which 82 per cent were carried to term. Without treatment, only 40 per cent of this group would be expected to have successful pregnancies.

Krohn (1941) administered oral anhydro-hydroxy-progesterone to 39 cases of threatened abortion, with successful results

TABLE 1.

PROGESTERONE IN TREATMENT OF THREATENED ABORTION

	No. of Cases	Successfully Treated	% Success	Treatment
Mason[67] (1942)	34	30	88%	Progesterone
Krohn[68] (1941)	39	32	82	Anhydro-hydroxy-progesterone
Collins[69] (1941)	24	21	88	Progesterone, vit. E, thyroid
Davis[70] (1942)	30	17	57	Progesterone, thyroid
Falls[71] (1942)	217	189	83	Progesterone
	234	206	88	Progesterone
	61	53	87	Progesterone
Javert[72] (1943)	10	8	80	Progesterone, vitamins, thyroid
Kotz[73] (1941)	139	64	46	Progesterone
Soule[74] (1941)	16	12	75	Progesterone, thyroid
Average percent success—			77.4%	

in 82 per cent. He comments on the advantages and convenience of oral therapy.

Reports in the literature since 1941 of investigators who used progesterone in treatment of threatened abortion, are shown in Table 1.

Habitual abortion differs from the spontaneous type in that there is a repetition of pathologically similar causes in two successive abortuses.[62] The treament of the two types of abortion need not differ except that in a known habitual aborter it is possible to institute prophylactic therapy at the time of conception. The rationale of this early elective therapy is based upon hormonal physiology cited in the second part of this paper, i.e., that any disturbance in the normal hormonal balance will be reflected in an incompletely prepared endometrium and myometrium causing an unfavorable maternal environment.

Malpas[75] believes that in a three-abortion sequence a common recurrent factor is responsible, and presents convincing logic that the chances of a live birth after such a sequence is only 1 to 3. Clinical experimentation on such a group of women will be valuable to determine the true effectiveness of therapy. McGregor and Stewart[76] recently reported a series of 11 women who had aborted three or four consecutive times. With progesterone treatment 8 of these women had normal pregnancies, while the statistical expectancy would be only 3 live births.

Krohn[68] (1941) presents a series of 11 women who had history of previous spontaneous abortion. Upon treatment with oral pregneninolone 10 of these produced live births. Kotz[73] reports a series of 17 cases in which there had been 53 previous pregnancies with only 8 live births. With progesterone treatments these 17 habitual aborters produced 16 full term deliveries, with no abnormal infants. Prophylactic therapy which can produce these results, even in such small series, deserves widespread clinical application.

Reports in the literature since 1940 of investigators who used progesterone in the treatment of habitual abortion are given in Table 2.

Judging from the literature, vitamin E is also of value in the treatment of habitual abortion and should be ultilized as a supplement to progesterone.

The importance of thyroid-gonad interrelationships has been emphasized previously. Authorities are unanimous in their opinion of thyroid administration in both spontaneous and habitual abortion. It is a widespread clinical observation that women with any signs of thyroid deficiency are apt to abort. In preconceptional treatment of habitual abortion, thyroid therapy is indicated in both partners if there is any evidence of thyroid hypofunction.

Vaux and Rakoff[44] (1945) used estrogen and progesterone in the treatment of habitual abortion, since they had noted that di-

TABLE 2.

PROGESTERONE IN THE TREATMENT OF HABITUAL ABORTION

	No. of Cases	Successfully Treated	% Success	Treatment
Buxton[77] (1940)	5	4	80%	Progesterone
Campbell[77] (1940)	13	11	85	Progesterone
Huber[78] (1940)	15	14	93	Progesterone
Collins[69] (1941)	12	9	75	Progesterone, vit. E, thyroid
Davis[70] (1942)	16	8	50	Progesterone, thyroid
Falls[71] (1942)	59	51	86	Lutein
	63	58	94	Lutein
	55	51	93	Lutein
Javert[72] (1943)	14	13	93	Progesterone, vit. E, thyroid
Kotz[73] (1941)	42	37	88	Progesterone
Krohn[68] (1941)	11	10	91	Anhydro-hydroxy-progesterone
Mason[67] (1942)	17	15	88	Progesterone
Average percent success—			84.6%	

minished blood and urine estrogen levels occurred as frequently as low pregnandiol titers. This therapy appears to have a rational basis in view of the fact that estrogen and progesterone concentrations parallel each other in gestation, both coming from the same source, and being involved in the normal metabolism of each other. They report a series of 24 habitual aborters who from 80 previous pregnancies had produced only 7 living babies (9 per cent). With estrogen and progesterone therapy there was a fetal salvage of 16 babies, or 67 per cent.

The fundamental importance of estrogen-progesterone metabolism has been demonstrated in practice by Karnaky.[79] He began to use stilbestrol in treatment of spontaneous and habitual abortion after having noted that this synthetic estrogen stopped labor pains of inevitable abortion almost immediately when injected into the anterior lip of the cervix. He reports 36 cases of threatened abortion treated by injection plus oral stilbestrol, with 92 per cent success. Habitual aborters also have responded to treatment with oral stilbestrol. The rationale of this form of therapy is associated with the metabolic interaction of estrogen and progesterone. From application of this previously discussed concept of normal physiology, the effect of stilbestrol in these patients was to increase the amount of estrogen degradation products which subsequently stimulated the ovarian or placental production of steroid hormones. It is unfortunate that the estrogen and pregnandiol levels of these patients were not carefully followed. Smith[80] (1946), however, has been able to demonstrate the progesterone-stimulating properties of diethylstilbestrol in human pregnancy. The results show in a very striking manner that while diethylstilbestrol was being taken the urinary excretion of pregnandiol rose steadily, and dropped precipitously each time it was omitted. For example, with increasing dosage of stilbestrol the urinary pregnandiol excretion was gradually raised to 70 mg. per twenty-four hours. On discontinuance of the therapy, the level fell almost immediately to 45 mg. per twenty-four hours. At this time, stilbestrol administration was reinstituted, and a marked response was evidenced by a subsequent pregnandiol excretion of 75 mg. per twenty-four hours, which was raised to even higher levels with increasing dosage of stilbestrol.

From the reports presented above, the value of hormonal therapy in threatened and habitual abortion is evident. It is obvious, however, that these reports were submitted because of their success, while possible failures of other workers remain unpublished. It appears that to establish more firmly the value of hormonal therapy in these cases, and to arrive at the most effec-

tive specific method of treatment, the following recommendations are in order:

(1) Adequate and fully accepted definitions of threatened and habitual abortion must be formulated.

(2) Numerous large series of cases must be obtained; each worker reporting the results of his specific method of hormonal treatment to an organized committee for statistical evaluation.

(3) Standard determinations of hormone levels in blood and urine must be made on each case before and after the institution of therapy to evaluate the indications for and results of the treatment.

(4) A thorough pathological examination should be made of each abortus.

Such a basic plan as this, with emphasis placed on the endocrine assays to show the physiologic results of treatment, will serve to firmly establish the rationale of hormonal therapy in abortion.

Surgery During Pregnancy: Surgical procedures in pregnant women always present the danger of abortion as a complication. When the necessary surgery is in close approximation to the internal genitalia the incidence of abortion is cited as approximately 5 to 10 per cent.[81] In view of the action of progesterone in inhibiting the motility of the pregnant uterus, it was suggested by Lackner and Tulsky[81] that the hormone might be used prophylactically in the postoperative therapy of pregnant women to decrease the consequent number of abortions. These workers reported a series of 9 women in which progesterone was used as postoperative therapy. None of the cases aborted. Recently Karnaky[79] has reported 100 per cent success in these cases by injection of stilbestrol before and after the operation. With larger series of cases, more adequately controlled, it certainly appears that the value of prophylactic hormonal therapy in surgery of gravid women can be firmly established.

Pregnancy Complicating Diabetes: Pregnancy in the diabetic is commonly complicated by preeclamptic toxemia, with associated fetal wastage. The use of insulin has reduced maternal mortality to an almost negligible figure, but the fetal mortality still ranges about 45 per cent.[82] In a series of 228 pregnant diabetic women, only 62 per cent delivered viable infants, 15 per cent of the pregnancies terminating in abortion or miscarriage and 23 per cent in stillbirths or neonatal deaths.[83,84]

On the basis of chorionic gonadotropin, pregnandiol and estrogen determinations, White and Hunt[84] classified 125 consecutive cases of pregnant diabetics as having a normal or abnormal balance of hormones. The main basis for a classification as abnormal was a rise in the level of chorionic gonadotropin during the twenty-fifth through the thirty-third week. Low estrogen and pregnandiol values were also classified as abnormal. Of the 125 cases 41 women had a normal hormonal balance, and in this group fetal survival was 95 per cent with no maternal toxemia noted. The other 77 cases were classified as having abnormal hormonal balances. The first 27 of this group received no therapy except insulin, and had a fetal survival of 60 per cent, toxemia in 52 per cent, and premature delivery in 40 per cent. The other 50 patients of the abnormal group were given estrogen and progesterone therapy in an attempt to correct the hormonal imbalance, resulting in a fetal survival of 92 per cent. On the basis of this study an imbalance of pregnancy hormones is definitely related to accidents characteristic of diabetic pregnancies, and estrogen and progesterone therapy is of great value in increasing the percentage of fetal survival.

From the previous discussion of steroid metabolism in normal pregnancy, it is logical to suspect that there is some abnormality of steroid metabolism underlying the pregnancy accidents of a diabetic. Smith and coworkers[85] have studied the steroid metabolism and levels of serum chorionic gonadotropin in a series of pregnant women with diabetes. Their report indicates that though an abnormal elevation of serum chorionic gonadotropin between the twenty-fifth and thirty-fifth weeks predicts later trouble, mishaps may also occur without any premonitary rise in chorionic gonadotropin.

A consistent finding in abnormal cases, however, is typical abnormality in the metabolism of the placental steroids. This change, starting as early as the eighteenth to twenty-eighth week, consists of a sudden increase in the rate of estrogen conversion, and a decrease in the rate of destruction. As we have seen previously, this situation of maximum production of steroids and maximum conversion of estrogens normally pertains two to three weeks before labor, resulting in progressive withdrawal of placental steroids.

It appears that this hormonal withdrawal is associated with pregnancy accidents of diabetics just as it is with the physiology of normal labor. Estrogen and progesterone therapy to correct this hormonal imbalance is physiologically rational and clinically effective.

Late Pregnancy Accidents Associated with Toxemia: Toxemias in the last trimester of pregnancy constitute a grave danger to both mother and child, the maternal mortality in eclampsia being approximately 13 per cent and the infant mortality 40 per cent.[86]

In 1933,[87] it was reported and confirmed that abnormally high levels of chorionic gonadotropin were present in both preeclamptic toxemia and eclampsia. Since this time it has been well established that a characteristic endocrine imbalance does exist in late pregnancy toxemia, essentially the same estrogen - progesterone deficiency which has previously been described in normal labor and diabetic pregnancy accidents.

Endocrine assays in patients whose pregnancies terminate during the third trimester in either premature labor, intrauterine death, preeclampsia or eclampsia indicates that a situation similar to that at term develops prematurely.[22,52,85] These patients show an early and abnormal peak during the second trimester in the levels of estrogen and pregnandiol, just as exists in the thirty-eighth week of normal pregnancy, characterized by a maximum conversion of estrogen and a minimum amount of estrogen breakdown products. Subsequently, there is a lack of placental stimulation with syncytial deterioration resulting in hormonal withdrawal and labor. In line with these hormonal findings is that pathological examination of the toxemic placenta shows typical syncytial degeneration just as in the normal placenta at term.[88] Why the placenta matures so early in toxemia has not yet been determined.

This abnormality in the metabolism of placental steroids is a constant finding in late pregnancy toxemia and associated accidents. Another quite constant and valuable finding has been a demonstrable abnormal elevation of chorionic gonadotropin.[88] In view of the fact that this principle begins to rise as estrogen and progesterone become progressively deficient, it appears that this high level may reflect failing utilization of this factor in their production.

The value of hormonal therapy in the analogous situation of late pregnancy accidents in diabetics has been amply proven. To date, however, such therapy in toxemia appears to be only promising, with much more investigation and study needed to prove its complete value. It appears that to be effective, replacement therapy must be initiated as early as the sixteenth week of pregnancy, before syncytial degeneration has occurred. Used as such a preventive measure, hormonal therapy may prove valuable in the treatment of late pregnancy toxemia.

One interesting aspect of investigation in this field which may prove valuable therapeutically, is the evidence presented by the Smiths of there being a toxic component of preeclampsia and eclampsia.[52] Toxicity has been demonstrated in the decidua from toxemic patients, and a similar fibrinolytic factor from the blood of toxemic women. It appears that this toxin may result from tissue catabolism following withdrawal of hormone support from the uterine contents, and the retention of it in the circulation responsible for the signs and symptoms of preeclamptic toxemia. Working upon the concept that the presence of this toxin prevents the normal response of the placenta to estrogen administration, attempts have been made to neutralize this factor. A pseudoglobulin fraction of menstrual discharge

and human exudative material has been found which protects rats against an otherwise lethal dose of this toxin. This is termed protective pseudoglobulin or PPs. Administration of PPs to six preeclamptic patients gave definite evidence of clinical benefit, including reduction of the hypertension, reduction of albuminuria, and loss of weight.[52]

Omission of PPs in the patients was followed by recrudescence of toxic signs. It was also noted that the fibrinolytic activity of the serum decreased as clinical improvement occurred. With the partial neutralization of this toxin, two of the patients responded to stilbestrol with a rise in urinary pregnandiol and a drop in serum chorionic gonadotropin. It appears that the degree of placental damage and the amount of circulating toxin are the two factors which influence the response of the placenta to stilbestrol administration. Thus the indications are that administration of PPs combined with diethylstilbestrol, instituted before degenerative changes in the placenta occur, may be of value in definitive therapy of toxemia. This is one of the many promising fields of endocrinology which deserves close experimental and clinical investigation.

SUMMARY

1. The chemistry and general physiological actions of the hormones concerned primarily with reproduction have been discussed. Emphasis has been placed on the coordinated interplay and interrelationships of these principles.

2. The hormonal physiology of normal pregnancy has been reviewed, accompanied by the results of endocrine assays in pregnancy and an integration of these hormones.

3. The importance of estrogen and progesterone metabolism has been emphasized and an interpretation given of the present pertinent knowledge concerning steroid metabolism, especially as it pertains to the maintenance of pregnancy.

4. Hormonal physiology in abnormal conditions of pregnancy, as determined by endocrine assays, has been discussed, and contrasted with the hormonal physiology of normal pregnancy. Endocrine abnormalities have been shown to exist in threatened and habitual abortion and in pregnancy accidents of diabetics and toxemic patients. The rationale of hormonal therapy in these patients has been discussed, and results of such therapy given. An optimistic outlook on hormonal therapy has been taken, with a view toward indicating the present value and future possibilities of prophylactic and therapeutic endocrinology in the field of fetal salvage.

REFERENCES

1. Kamm, O., *et als*: J. Am. Chem. Soc. 50:573, 1928.
2. Van Dyke, H. B., Chow, B. F., Greep, R. O., and Rothen, A.: Am. J. Physiol. 133:473, 1941.
3. Riddle, O.: Glandular Physiol. & Therap., A.M.A., Chicago, 1942.
4. Best, C. H. & Taylor, N. B.: The Physiological Basis of Medical Practice, Williams & Wilkins, Balt., 1945.
5. White, A., Catchpole, H. R., and Long, C. N. H.: Science 86:82, 1937 (cited by White in Protein Hormones of the Pituitary Body, Ann. N. Y. Acad. Sci. 53:344, 1943).
6. Collip, J. B., and Anderson, E. M.: Lancet 1:76, 1934.
7. Crowe, S. J., Cushing, H., and Homans, J.: Bull. John Hopkins Hosp. 21:127, 1910.
8. Fevold, H. L., Hisaw, H. W., Hellbaum, A., and Hertz, R.: Am. J. Physiol. 104:710, 1933.
9. Li, C. H., Simpson, M. E., and Evans, H. M.: Endocrinol 27:803, 1940.
10. Eagle, E. T.: Am. J. Physiol. 106:145, 1933.
11. Cole, H. H., and Hart, G. H.: Am. J. Physiol. 93:57, 1930.
12. Hoffman, J.: Female Endocrinology, W. B. Saunders Co., Phila., 1944.
13. Hertz, R., and Hisaw, F. L.: Am. J. Physiol. 108:1, 1934.
14. Casida, L. E.: Endocrinol. 18:714, 1934.
15. Fevold, H. L.: Endocrinol. 28:33, 1941.
16. Rakoff, A. E.: Hormone Assay and Endocrine Function, XXIV, pp. 524-66 in Cantarow, A. & Trumper, M.: Clinical Biochemistry 3rd ed., Saunders, Phila., 1945.
17. Schering Corp.: Sex Endocrinology, Schering Corp., Bloomfield, N. J., 1944.
18. Dodds, E. C., Goldberg, L., Lawson, W., and Robinson, R.: Nature 142:34, 1938.
19. Segaloff, A.: J. Clin. Endocrinol. 4:199, 1944.
20. Pincus, G., & Pearlman, W. H.: Vitamins and Hormones, Academic Press, New York, Vol. 1, 1943.
21. Cantarow, A., Rakoff, A. E., Paschkis, K. E., and Hansen, L. P.: Proc. Soc. Exp. Biol. Med. 49:707, 1942.
22. Smith, O. W., Smith, G. V. S., & Schiller, S.: J. Clin. Endocrinol. 1:461, 1941.
23. Rakoff, A. E., Paschkis, K. E., and Cantarow, A.: Am. J. Obst. and Gyn. 46:856, 1943.
24. Szego, C. M., and Roberts, S.: Endocrinol. 41:323, 1947.
25. Cohen, S. L., Marrian, G. F., and Watson, M.: Lancet 1:674, 1935.
26. Corner, G. W., and Allen, W. M.: Am. J. Physiol. 88:326, 1929.
27. Lyon, R.: Am. J. Obst. and Gyn. 51:403, 1946.
28. Venning, E. H., and Browne, J. S. L.: Proc. Soc. Exp. Biol. N. Y. 38:503, 1938 (cited by Cope, No. 30).
29. Guterman, H. S.: J. Clin. Endocrinol. 4:262, 1944.
30. Cope, C. L.: Clinical Science 4:217, Oct., 1940.
31. Venning, E. H., and Browne, J. S. L.: Endocrinol. 21:711, 1937.
32. Catchpole, H. R., Hamilton, J. B., and Hubert, G. R.: J. Clin. Invest. 22:799, 1943.
33. Brown, W. E., and Bradbury, J. T.: Am. J. Obst. & Gyn. 53:749, May, 1947.

34. Browne, J. S. L., Henry, J. S., and Venning, E. H.: Am. J. Obst. & Gyn. 38:927, 1939.

35. Rakoff, A. E.: M. Clin North America 26:1915, (November) 1942.

36. Seegar Jones, G. E., Gey, G. O., and Gey, M. K.: Bull. Johns Hopkins Hosp. 72:26, 1943.

37. Zondek, B.: Klin. Wchnschr. 10:2121, 1931 (cited by Hoffman, No. 12).

38. Severinghaus, A. E.: Physiol. Rev. 17:566, 1937.

39. Harrow, B.: Textbook of Biochemistry, 3rd ed., Saunders, Phila., 1945.

40. Smith, G. V. S., and Smith, O. W.: Am. J. Obst. and Gyn. 38:618, 1939.

41. Corner, G. W.: Hormones in Human Reproduction, Princeton Univ. Press, 1947.

42. Ask-Upmark: Acta. obstet. gynec., scand., 5:211, 1926 (cited by Cope, No. 30).

43. Pratt, J. P.: Endocrinol. 11:195, 1927.

44. Vaux, N. W., and Rakoff, A. E.: Am. J. Obst. and Gyn. 50:353, 1945.

45. Novak, E.: J. Clin. Endocrinol. 3:274, 1943.

46. Hisaw, F. L.: Physiol. Zool. 2:59, 1929 (cited by Hoffman, No. 12).

47. Zarrow, M. X.: Endocrinol. 42:129, 1948.

48. Chu, J. P.: J. Endocrinol. 4:109, 1945.

49. Murphy, D. L.: Am. J. Obst. and Gyn. 42:281, 1941.

50. Heckel, G. P., and Allen, W. M.: Am. J. Physiol. 123:353, 1934.

51. Karnaky, K. J.: Am. J. Obst. and Gyn. 53:312, 1947.

52. Smith, O. W., and Smith, G. V. S.: West. J. Surg., Obst. and Gyn. 55:313, June 1947.

53. Smith, G. V. S., and Smith, O. W.: Am. J. Physiol. 98:578, 1931.

54. Pincus, G., and Zahl, P. A.: J. Gen. Physiol. 20:879, 1937.

55. Smith, G. V. S., and Smith, O. W.: Am. J. Obst. and Gyn. 39:405, 1940.

56. Burrows, H.: Biological Actions of Sex Hormones, Cambridge Press, 1945.

57. Smith, O. W.: Endocrinol. 35:146, 1944.

58. Segaloff, A.: Endocrinol. 42:15, January 1948.

59. Segaloff, A.: Personal communication, 1948.

60. Hertig, A. T., and Edmonds, E. W.: Arch. Path. 30: 260, 1940.

61. Mall, F. P., and Meyer, A. W.: Contributions to Embryology, Vol. XII, Carnegie Institute, 1921 (cited by Hertig, No. 62).

62. Hertig, A. T., and Livingstone, R. G.: New Eng. J. M. 230:797, 1944.

63. Council of Pharmacy and Chemistry, J.A.M.A., 114: 2214, 1940.

64. Taussig, F. J. B.: Abortion, Spontaneous and Induced: Medical and Social Aspects, St. Louis, C. V. Mosby Co., 1936.

65. Dunn, H. L.: Frequency of Abortion; Its Effect on Maternal Mortality Rates, I, pp. 1-14 in The Abortion Problem: Williams and Wilkins, Balt., 1944.

66. Hudgins, A. P.: Med. Times 71:147, 1943.

67. Mason, L. W.: Am. J. Obst. and Gyn. 44:630, 1942.

68. Krohn, L., and Harris, J. M.: Am. J. Obst. and Gyn. 41:95, 1941.

69. Collins, C. G., Weed, J. C., and Collins, J. H.: Surg., Gyn. and Obst. 70:783, 1940.

70. Davis, C. D., Hamblen, E. C., Cuyler, W. K., and Baptist, M.: J. Clin. Endocrinol. 2:377, 1942.

71. Falls, F. H., Rezek, G. H., and Benensohn, S. J.: Surg., Gyn. and Obst. 75:289, 1942.

72. Javert, C. T., and Stander, H. J.: Surg., Gyn. and Obst. 76:115, 1943.

73. Kotz, J., Parker, E., and Kaufman, M. S.: J. Clin. Endocrinol. 1:838, 1941.

74. Solue, S. D.: Am. J. Obst. and Gyn. 42:1009, 1941.

75. Malpas, P.: J. Obst. and Gynec. Br. Empire, 45:932, 1938 (cited by Engle, E. T., in The Abortion Problem: William and Wilkins, Balt., 1944).

76. McGregor, T. N., and Stewart, C. P.: J. Obst. and Gynec. Br. Empire, 46:857, 1939 (cited by Engle, E. T., in The Abortion Problem: William and Wilkins, Balt., 1944).

77. Buxton, C. L.: Am. J. Obst. and Gyn. 40: 202, 1940.

78. Campbell, R. E., and Sevringhaus, E. L.: Am. J. Obst. and Gyn. 39:573, 1940.

79. Karnaky, K. J.: So. M. J. 35:838, 1942.

80. Smith, O. W., Smith, G. V. S., and Hurwitz, D.: Am. J. Obst. and Gyn. 51:411, 1946.

81. Lackner, J. E., and Tulsky, A. S.: Am. J. Surg. 46: 362, 1939.

82. Nothmann, M.: New Eng. J. Med. 64:275, 1941 (cited by Hoffman, No. 12).

83. White, P., and Hunt, H.: J.A.M.A. 115:2039, 1940.

84. White, P., and Hunt, H.: J. Clin. Endocrinol. 3:500, 1943.

85. Smith, O. W., Smith, G. V. S., and Hurwitz, D.: Am. J. Med. Sciences 208:25, 1944.

86. DeLee, J. B., and Greenhill, J. P.: Principles and Practice of Obstetrics, Saunders Co., Phila., 1947.

87. Smith, G. V. S., and Smith, O. W.: Proc. Soc. Exper. Biol. and Med. 30:918, 1933.

88. Smith, G. V. S., and Smith, O. W.: West. J. Surg., Obst. and Gyn. 55:288, May, 1947.

NEW ORLEANS
Medical and Surgical Journal

Established 1844

Published by the Louisiana State Medical Society under the jurisdiction of the following named Journal Committee:

George W. Wright, M. D., Ex-Officio
E. L. Leckert, M. D., Chairman
C. M. Horton, M. D., Vice-Chairman
Sam Hobson, M. D., Secretary
Edwin H. Lawson, M. D.
Leon J. Menville, M. D.

EDITORIAL STAFF

Philip H. Jones, M. D.....*Editor*

COLLABORATORS—COUNCILORS

H. Ashton Thomas, M. D.
Joseph S. Kopfler, M. D.
Guy R. Jones, M. D.
Paul D. Abramson, M. D.
C. Prentice Gray, Jr., M. D.
W. E. Barker, Jr., M. D.
J. W. Faulk, M. D.
O. B. Owens, M. D.

C. Grenes Cole, M. D.....*General Manager*
1430 Tulane Avenue

SUBSCRIPTION TERMS: $4.00 per year in advance, postage paid, for the United States; $4.50 per year for all foreign countries belonging to the Postal Union.

News material for publication should be received not later than the eighteenth of the month preceding publication. Orders for reprints must be sent in duplicate when returning galley proof.

Manuscripts should be addressed to the Editor, 1430 Tulane Ave., New Orleans, La.

THE JOURNAL *does not hold itself responsible for statements made by any contributor.*

DDT
DICHLORODIPHENYLTRICHLORETHANE
CHLOROPHENOTHANE U. S. P.

DDT is the abbreviated name of various mixtures of isomers of dichlorodiphenyltrichloroethane. The chemical has come into wide use in the past ten years, and was employed extensively by the armed forces as an insecticide during World War II and in recent years. The spread in use of this substance appears to be increasing. With this in mind, the Council on Pharmacy of the A. M. A. has just issued a report of the Committee on Pesticides, covering the various aspects of DDT.

When first introduced the report quickly became current that DDT was toxic and effective for insects, and harmless for man,—or nearly so. The facts presented in the report referred to above show clearly that its toxicology has an important bearing in clinical medicine, and that those who have immediate, or even occasional contact with the preparation should be aware of its effects

Chemical or commmerical DDT is a soft, cream to gray powder with a fruitlike odor. Its properties of solubility are of importance clinically. It is not soluble in water, but moderately soluble in mineral and vegetable oils, and readily soluble in most common organic solvents.

For insecticidal use, it is prepared in oil solutions; in emulsion concentrates; in powders incorporated into suitable dry carriers for application as a dust; in aerosols in suitable oils for dispersion; and coverings, included in paints, polishes and waxes. The form of preparation depends upon the type of use, the coverage desired, the pest, and the area or location where control is desired. Concentrations used vary from 1 to 75 per cent in these various preparations.

It is used as a contact and stomach poison. It is not a fumigant or repellant, nor does it have ovicidal properties. It acts primarily on the nervous system of the insect. Some species, notably houseflies and certain mosquitoes, have developed a tolerance or resistance to DDT. The agent is comfortably used in the control of many plant pests, including species attacking fruit, shade and forest trees, ornamentals, vegetables, field and grain crops. It should be applied cautiously to food crops of the type that require treatment with it after the development of the edible portion of the plant. It has also been used in the control of pests of livestock and other domesticated animals. It should not be used on dairy cattle or on animals being prepared for slaughter.

In therapeutics, DDT is used as a pediculicide and in conjunction with benzyl benzoate and ethylaminobenzoate as a pediculicide and scabicide.

The pharmacological effect is a cerebrospinal poison, acting primarily on the cen-

tral nervous system in higher animals and in man, as contrasted with its apparent peripheral action in insects. The cerebellum and the higher motor cortex appear to be the chief sites of action. Its effect on the myocardium is such that ventricular fibrillation may be induced. Absorbability is thought to be the principal factor which differentiates the toxicidity of DDT in insects from that in man. It can be absorbed through the gastrointestinal tract, the respiratory tract, and through the skin. Retention in the respiratory tract depends largely upon the size of the particle. Absorption from the gastrointestinal tract and skin is also influenced by the solvent used. When applied as wettable powders to dairy cows, it appeared in body fat and milk.

Excretion of DDT is slow and incomplete. A part of the chemical remains unchanged, stored throughout the body in fat depots from which it is gradually released.

After absorption DDT is found in all tissues, but because it is more soluble in fat, the greatest amounts are evenly distributed among the fat deposits of the body. Such an accumulation continues according to the size of the dose and the length of contact. The amount stored may be 6 to 28 times the dietary intake. With low dosage levels, a maximum storage level is reached in six months. An animal may, therefore, accumulate amounts equivalent to several intravenous lethal doses without showing any obvious signs of poisoning. A lethal dose by the intravenous route is 50 mg. per kilogram for most species. In man, the fatal oral dose is not known. As a result of observation on one fatality, it may be about 500 mg. per kilogram. Powdered DDT rarely is toxic or irritating to the intact skin. DDT solution is poisonous. Moderate transient contact with DDT solutions of low concentration (5 per cent and under) will not be dangerous, but prolonged, heavy exposure should be avoided. Danger lies in handling concentrated solutions of 10 per cent to 25 per cent.

The solvents in which the agent may be dissolved are themselves a source of toxic effect, such as petroleum distillates and other organic solvents.

The inhalation of DDT powder offers little hazard because of the large particle size and the relative insolubility of the compound. Mixed with wetting agents, an irritant and toxic effect may be produced on the bronchi. Emulsions and oral solutions may be readily absorbed by the lungs on inhalation. Appreciable concentrations of the insecticide do not stay long in the atmosphere. For this reason, a concentration of DDT of 12 to 50 mg. per liter of air from the use of the standard DDT aerosol 3 per cent solution will not produce symptoms of poisoning.

The symptoms may be those of acute poisoning or chronic poisoning. In the acute form there are described twitchings of the eyelids, tremors beginning in the muscles of the head and neck and progressing caudally to involve the entire musculature. This may become severe in the extremities. Convulsive seizures similar to strychnine poisoning may be elicited by irritation and mechanical stimuli. Death may result from respiratory failure or heart failure.

Chronic intoxication may present symptoms common to such poisons whose action is long continued. These are loss of weight, anorexia, mild anemia, muscle weakness, and tremors. Diagnosis would be based primarily on a history of exposure and the clinical findings mentioned above. These may be supported in part by evidences of liver damage, as shown by the various liver function tests.

The solvents which carry the chemical may produce a similar toxic picture. The effect of these solvents is noted promptly; whereas that of DDT appears after some hours.

The treatment of the condition is directed towards removing the chemical from the alimentary tract, and symptomatic medication for the neurological symptoms. Phenobarbital should be administered in sufficient dosage to control the tremor. Administration of epinephrine is to be avoided because of its possible effect in bringing on ventricular fibrillation in this condition.

Precautions should be considered as occupational and household. The skin should be protected against oily solutions. When

the clothes are contaminated they should be changed. Those exposed to the dust in the absence of free movement of air currents should use respirators. Operators using large scale spraying or fogging machines should wear respirators.

Household precautions are that the chemical should never be stored in food cupboards or in medicine chests where a mistake may occur. Exposed foods and utensils must be covered when the kitchen is being sprayed. Use of oil solutions or inflammable preparations in the presence of open fires should be avoided.

Three hundred and eighty-four cases of poisoning have been tabulated. Fourteen deaths are recorded.

Under conditions of adequate care, DDT is not likely to be harmful. Without due regard to its toxic possibilities poisoning may occur.

ORGANIZATION SECTION

The Executive Committee dedicates this section to the members of the Louisiana State Medical Society, feeling that a proper discussion of salient issues will contribute to the understanding and fortification of our Society.

An informed profession should be a wise one.

ANNUAL MEETING

The physicians of the Orleans Parish Medical Society are very pleased that the 1951 Annual Meeting of the Louisiana State Medical Society is to be held in New Orleans.

The Committee on Arrangements has been very busy the past few months making plans for the meeting this year. On the entertainment side, plans have been made for a Golf Tournament to be held at the Metairie Country Club. A letter giving full details on the tournament has been sent to the members.

A dinner-dance will be held on Tuesday, May 8, from 9 p. m. to 1 a. m. in the Grand Ball Room of the Roosevelt Hotel. The A. S. Aloe Company has planned a Cocktail Party for members, their wives, and guests on Tuesday, May 8, from 5 to 7 p. m. There will be a luncheon for members of the House of Delegates on Monday, May 7.

Scientific Exhibits are to be placed in the University Room and other meeting rooms at the Roosevelt. A letter soliciting exhibits has been sent to every member of the State Society.

Plans are being made for a medical section and a surgical section on Tuesday, May 8, with specialty groups on Wednesday. Several out of state speakers have accepted invitation to participate in the program.

Pharmaceutical companies, drug houses, instrument houses, and other companies have cooperated by buying technical exhibit space and the display will prove most interesting and attractive to the doctors in attendance.

Hotel reservations are being handled through the Office of the Secretary-Treasurer. You are urged to get your request for reservations in early.

A cordial welcome from the Orleans Parish Medical Society is extended to all.

M. M. HATTAWAY, M. D., *Chairman*
Committee on Publicity

THE SIXTH RURAL HEALTH CONFERENCE OF THE AMERICAN MEDICAL ASSOCIATION, HELD IN MEMPHIS, TENNESSEE, FEBRUARY 22 THROUGH 24, 1951

Probably the most successful conference held by the American Medical Association was completed in Memphis, Tennessee, February 22-24, 1951. There was a total registration of approximately 600 and practically every organization in the United States interested in rural health was represented.

This was the sixth yearly conference held by the AMA and the first one to be held in the South. It was preceded by a Secretaries' and Presidents' Conference on Feb-

ruary 22. The enthusiasm of the conference left no doubt in anybody's mind that the health of the rural people is foremost in the minds of those who are responsible for giving rural people better medical care. The Secretaries' and Presidents' conference also attended by representatives of the Extension Services of most of the state universities was highlighted by the talk of Aubrey D. Gates, field director on the rural health committee for the AMA. In his talk, he stressed the responsibility of the rural people and the physicians in the community for giving good medical care. Among other things, he pointed out that rural people are willing and anxious to take on the responsibility of providing facilities whenever they know and understand what the responsibilities are.

Mr. Gates has travelled over thirty-four of our forty-eight states and has appeared before state and rural health councils. He has talked with lay and professional leaders on rural health problems all over the country and is probably the best informed man in the American Medical Association on rural medical affairs. Everyone was asked to participate in his discussion and many highlights of a local nature were brought out.

The rural health conference itself which started on February 23 was opened with a full attendance. The AMA was represented by Dr. Elmer Henderson, president, Dr. George F. Lull, secretary-treasurer, Dr. Howard, Editor of the J. A. M. A., and a full attendance of the rural health committee. Rural health committees of the Farm Bureau, the Grange, the Milk Producers' Association, Associated Women's Farm Bureau, American Academy of General Practice, the editors of the Farm Journals and many other organizations were represented. There was probably never such a large array of talent, interested in rural health, assembled in one audience.

The theme of the conference, "Why Wait —Let's Do It Ourselves," was carried throughout the whole conference. Dr. E. K. Yantes, of Wilmington, Ohio, went into detail about how Clinton County, Ohio, had gone about solving its own problems. He stated that the first thing they did was make a survey of the county and this was done by the people themselves. They found out what their problems were, what things they were lacking and now are at work on solving these problems.

One of the outstanding portions of the first day's program was the skit on "Who Is Going To Do It?" This was a non-rehearsed version of how to form a rural health council by representatives of the local medical societies, County Agent, the local health nurse, Milk Producer's Association, and the Parent-Teacher's Association. It showed how a group of people interested in solving the problems in good medical care may go about forming their own council.

The first day's program was high-lighted at the night meeting by two speeches: one by Dr. Haven Emerson, Professor-emeritus of Columbia University, New York, "The Grand Old Man Of Public Health;" and the other by Mrs. Charles W. Sewell, the "Sweetheart of Rural America." Mrs. Sewell talked on "Let's Try the American Way" and pointed out the various ways in which rural America can help itself.

The last day of the conference, February 24, was extraordinary throughout. The first portion of the program had such outstanding persons as our own H. C. Sanders of the L. S. U. Extension Service, Mrs. Arthur A. Herold, president of the Woman's Auxiliary of the AMA and others. But the morning was topped by "Plan For Rural Medical Services" by Dr. George F. Bond of Bat Cave, North Carolina. His speech was preceded by a motion picture with sound made by the AMA in which Dr. George Bond was the central figure and the principal actor. It illustrated how a rural physician in the mountains of North Carolina, a section without a doctor in many years, could go in, build a twelve bed hospital, equip it with the latest facilities for good medical care and carry on a good medical service. The labor and materials were donated by the people of the community and the hospital was constructed and equipped at a cost of $1200 per bed. It illustrates how a rural practice can be carried on more efficiently

in a jeep and how the patients themselves can be trained to come in to the clinic hospital for their medical care thereby saving the doctor's time and physical endurance for the better medical care of his patients. This film was made at a cost of over $100,000 and is available from the AMA for general use.

The meeting closed on February 24 in the afternoon with three talks that were outstanding. The first was by Dr. Dean S. Luce, "The General Practitioner of the Year" from Canton, Massachusetts. He emphasized the joys and pleasures, along with the heartaches and pains, of being a general practitioner. Dr. Elmer Henderson, president of the American Medical Association, followed with an important talk on medical care of America without government interference. Then Ed Lipscomb of the National Cotton Council wound up the conference with a terrific story on how we can solve our own problems without meddlesome interference from Washington and how private initiative is always superior to government control and how we can solve our own problems if we will only set ourselves to it.

The Louisiana State Medical Society was represented by Dr. Guy R. Jones of Lockport, and your reporter.

J. P. SANDERS, M. D.

LOUISIANA STATE MEDICAL SOCIETY NEWS

CALENDAR

PARISH AND DISTRICT MEDICAL SOCIETY MEETINGS

Society	Date	Place
East Baton Rouge	Second Wednesday of every month	Baton Rouge
Morehouse	Third Thursday of every month	Bastrop
Natchitoches	Second Tuesday of every month	
Orleans	Second Monday of every month	New Orleans
Ouachita	First Thursday of every month	Monroe
Rapides	First Monday of every month	Alexandria
Sabine	First Wednesday of every month	
Second District	Third Thursday of every month	
Shreveport	First Tuesday of every month	Shreveport
Vernon	First Thursday of every month	

MEETING OF THE AMERICAN GOITER ASSOCIATION

The American Goiter Association meeting will be held in the Deshler-Wallick Hotel, Columbus, Ohio, on May 24, 25 and 26, 1951. The program for the three day meeting will consist of papers dealing with goiter and other diseases of the thyroid gland, dry clinics and demonstrations.

ANNOUNCEMENT OF MEETINGS

Several meetings of interest to scientists and physicians will be held at the Texas Medical Center, Houston, Texas, on April 20 and 21.

These will include the *Fifth Annual Symposium on Fundamental Cancer Research* of The University of Texas M. D. Anderson Hospital for Cancer Research. One half day will be devoted to selected papers on the subject of protein metabolism in cancer. The *Cancer Pathology Conference* of The University of Texas Postgraduate School of Medicine will be concerned primarily with breast cancer. An assortment of other tumors will be discussed, however. *A South Central Region Meeting of the College of American Pathologists*, with coparticipation in the Symposium and Pathology Conference, will be held. Papers of general interest to pathologists will be included on this program.

IN MEMORIAM

Whereas, through the untimely death of Dr. B. E. Nelken, the Secretary to the East Baton Rouge Parish Medical Society, the members have suffered the loss of one of their most esteemed and highly regarded colleagues; and

Whereas, this physician, whose life of selfless service and devotion to the ideals and practice of medicine reflected honor upon all those who shared his profession; and

Whereas, his tireless battle against pain and disease was a source of comfort and courage to his many patients, and an inspiration to this community, whose health he sought without thought of acclaim or reward; therefore be it

Resolved: That the members of the East Baton Rouge Parish Medical Society express their heartfelt sympathy to the family of Dr. Nelken, and that a copy of this resolution be spread on the minutes as a tribute to his memory.

Resolutions Committee,
Arthur D. Long, M. D., Chairman.
East Baton Rouge Parish Medical Society.
February 13, 1951.

ANNUAL MEETING

The first annual meeting of the Eye, Ear, Nose and Throat Hospital Alumni Association will be held in New Orleans, April 26, 27, and 28, 1951. All physicians who have received their specialty training at the Hospital are cordially invited to attend.

One day will be devoted to ophthalmology and another to otolaryngology. On the morning of Saturday, April 28, 1951, there will be demonstrations of a number of operative procedures in each specialty.

Each night there will be a cocktail party. During the day the wives of the Alumni will be entertained at tea, taken on tours of homes in New Orleans' famed French Quarter and Garden District, and taken on a yacht trip on the Mississippi River during which a buffet luncheon will be served.

Please address all inquiries to George H. Hauser, M. D., 145 Elk Place, New Orleans, Louisiana.

MEDICAL SEMINAR IN CARDIOVASCULAR DISEASES

The Mount Sinai Hospital of Greater Miami will hold its First Annual Medical Seminar in Cardiovascular Diseases at The Sorrento Hotel, May 23, 24 and 25, 1951. All of those interested may obtain further information by writing to Chairman, Seminar Committee, Mount Sinai Hospital, 4300 Alton Road, Miami Beach, Florida.

PHYSICIANS' ART SHOW AT AMERICAN MEDICAL ASSOCIATION MEETING ATLANTIC CITY

The American Physicians Art Association will have an art exhibit, as usual, during the A. M. A convention at Atlantic City, N. J., June 11 to 15, 1951, inclusive. Any physician in the United States, Canada and Hawaii desiring to participate in this show should communicate with the secretary, F. H. Redewill, M. D., 760 Market Street, San Francisco 2, California, for particulars.

J. Henry Helser & Co., Inc., Investment Managers with offices on the Pacific Coast, are the new sponsors of the American Physicians Art Association and will award 200 trophies besides a special Helser Trophy—a large decorative cup depicting Yankee Ingenuity. This cup is to be awarded for art work done in any medium. Also the large Popularity Trophy will be awarded to the owner of the art piece receiving the most popular votes during the A. M. A. convention. Over 4000 members of the American Physicians Art Association will receive shortly, entry blanks, shipping labels and rules about this fourteenth art exhibition.

The Annual Art Banquet will be held Tuesday evening, June 12 at the Marlborough-Blenheim Hotel, Atlantic City, N. J.

SEVENTEENTH ANNUAL MEETING OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

The seventeenth annual meeting of the American College of Chest Physicians will be held at the Ambassador Hotel, Atlantic City, New Jersey, June 7 through 10, 1951. An interesting scientific program has been arranged for presentation at the meeting.

The Board of Examiners of the College has announced that the next oral and written examinations for Fellowship will be held in Atlantic City on June 7. Candidates who would like to take the examinations for Fellowship should contact the Executive Secretary, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

The Convocation ceremonies will be held at the Ambassador Hotel, Atlantic City on Saturday, June 9, at which time Certificates will be awarded to new Fellows of the College.

Dr. Alton Ochsner, New Orleans, is Governor of the College for Louisiana.

WOMAN'S AUXILIARY TO THE LOUISIANA STATE MEDICAL SOCIETY

EAST BATON ROUGE

A gay Mardi Gras theme carried out with the official carnival colors, balloons and confetti, highlighted the February meeting of the Woman's Auxiliary, held at the Woman's clubhouse, Mrs. Marion Kofler, President, presiding. The business session was followed by a book review by Mrs. James O. Mullino—*Anybody Can Do Anything* by Betty McDonald.

Mrs. John Ray Powers acted as hostess, assisted by the following committee: Mrs. Dionysius Cacioppo, Mrs. David VanGelder, Mrs. Rhett McMahon, Mrs. William Moody, Mrs. Lloyd G. Perez, Mrs. Jacob O. Hoth, Mrs. Henry Hatcher, Mrs. H. S. Morris, Mrs. Roy Rabalais, Mrs. Joseph Noto, Mrs. Myron Walker, and Mrs. Robert Hansen.

The Easter motif was carried out in varied detail at the March meeting of the Women's Auxiliary to the East Baton Rouge Parish Medical Society at the Woman's clubhouse.

On the stage an "Easter Parade" of spring hats had been arranged, with the House of Fashion serving as the sponsoring store.

During the meeting reports on social agencies such as the March of Dimes were given and the members' participation in the March of Dimes, Cancer, Community Chest and Crippled Children's drives listed.

Mrs. Paul Marks was chairman of the hostess committee, whose members were: Mrs. Charles Mosely, Jr., Mrs. George Dicks, Mrs. F. A. DeJean, Mrs. J. R. Godfrey, Mrs. J. J. LaNasa, Mrs. Paul Landry, Mrs. David S. Malen, Mrs. Melvin Schudmak, Mrs. F. W. Pickell, Mrs. Charles Voss, Mrs. Lester Williams and Mrs. D. J. Fourrier.

LAFAYETTE PARISH

The Auxiliary discussed plans and began preparations for "Doctors' Day" March 29, at a meeting held at the home of Mrs. I. H. Robinson with Mrs. Thomas Latiolais as co-hostess.

Dr. Kenneth Hait was guest speaker at the meeting and talked on "The Emotions." He cited case histories illustrating how the ordinary acts of our every day living are motivated by emotions. Understanding these underlying emotions is a step in maintaining good mental health.

Following Dr. Hait's address refreshments were served. Attending the meeting were Mmes. Edward W. Wynne, Tom Kimbrough, Ed Breaux, R. D. Voorhies, L. A. Prejean, Stanley Morgan, Lee Sonnier, James Gilly, Sidney Hernandez, Boring Montgomery, Ralph Bourgeois and Douglas Chesson.

ORLEANS PARISH

The wives of the visiting physicians in New Orleans for the fourteenth annual meeting of the New Orleans Graduate Medical Assembly were the guests of honor at the monthly program-reception of the Woman's Auxiliary of the Orleans Parish Medical Society, at the Orleans Club. Mrs. Otto Schwartz gave a dramatic reading. Pouring tea were Mrs. J. Kelly Stone, and the president, Mrs. John T. Sanders.

Mrs. Edwin Guidry, essay chairman, reported that the contest was well under way and that the response had been especially good. Mrs. J. W. Warren announced that the State Judges for the contest are Dr. E. L. Leckert, of the Louisiana State Board of Medical Examiners; Dr. John B. Entrekin, head of the department of Chemistry, Centenary College, Shreveport; Mrs. Samuel Levy, of Natchitoches, past president of the Louisiana State Federation of Women's Clubs; Dr. C. C. Henson, Executive Consultant to the Edward J. Schlieder Educational Foundation; Dr. Wilson C. Wolfe, of Ottumiva, Iowa, National Chairman of the AAPS committee, who visited New Orleans during the New Orleans Graduate Medical Assembly and conferred with Mrs. Guidry at that time is in favor of a special prize for seventh and eighth grade pupils.

Mrs. Joseph S. D'Antoni, general chairman, announced appointment of committee chairmen for the coming State Society Convention in May:

Mrs. C. Grenes Cole, Mrs. Charles B. Odom, Vice-Chairmen;

Honorary Committee: Mrs. George Wright, Mrs. John Sanders, Mrs. DeWitt T. Milam, Mrs. Boni DeLaureal.

Chairmen of Subcommittees: Mrs. Boni DeLaureal, Registration; Mrs. Alberto Prieto, Information and Tickets; Mrs. William Sodeman, Publicity; Mrs. George Feldner, Transportation; Mrs. Edwin Guidry, Transportation; Mrs. Louis Leggio, Flowers; Mrs. Eugene Countiss, Tea; Mrs. Jules Myron Davidson, Luncheon; Mrs. T. T. Gately, Tea Girls; Mrs. Roy B. Harrison, Printing; Mrs. Jerome Landry, Pages; Mrs. Robert Kelleher, Finance.

Mrs. Wm. A. Sodeman,
Publicity Chairman

A. M. A. MEETING

A few more months, and the members of the Woman's Auxiliary to the American Medical Association will be arriving in Atlantic City, New Jersey, for their annual Convention June 11-14.

Have you made your reservations? If not, send your request *at once* to Dr. Robert A. Bradley, Chairman, A. M. A. Housing Bureau, 16 Central Pier, Atlantic City, New Jersey.

BOOK REVIEWS

Thoracic Surgery: By Richard H. Sweet, M. D. Philadelphia, W. B. Saunders Company, 1950. Pp. 345. Price, $10.00.

This concise yet very complete monograph is excellently planned, clearly written and well illustrated. The material is presented in a logical and orderly fashion beginning with surgical anatomy and proceeding with detailed discussions of indications for thoracic surgery, preoperative and postoperative management, and those operative technics which the author has found to be useful in everyday practice. In the preface the author states, "The present volume is based upon the concept that any properly qualified surgeon can acquire with relative ease a satisfactory proficiency in thoracic surgery by employing the technics herein described," but he adds, "The wide scope of material presented necessitates the description of procedures which involve a familiarity not only with the thorax but also with the neck and abdomen."

Ambrose H. Storck, M. D.

A Textbook of X-Ray Diagnosis: By S. Cochrane Shanks, M. D., F. R. C. P., F. F. R., and Peter Kerley, M. D., F. R. C. P., F. F. R., D. M. R. E. London, W. B. Saunders Co., 1950. Pp. 574. Price $18.50.

Volume IV is the first volume published of the Second Edition of an outstanding and extremely valuable work on diagnostic radiology. The first edition, which was published ten years previously, was a remarkable success and was reprinted five times during the ten year period.

With few exceptions, the same group of distinguished British authors have contributed to the present volume. The rather marked increase in knowledge has necessitated the expansion from the original three volumes to the present four volume work.

The present volume is devoted to the bones and joints and soft tissues and is divided into eleven parts. Part One is concerned with normal bones and joints and covers the more common variations of the normal. The general pathology of bone is considered in Part Two. The next seven parts cover the various classifications of bone lesions. Part Ten is devoted to the soft tissues and foreign body localization is covered in Part Eleven.

In general the text is well written and the illustrations are unusually good. When all volumes of the set become available it should serve as a valuable reference.

J. N. Ané, M. D.

Light Therapy: By Richard Kovacs. Springfield, Charles C. Thomas, Publisher, 1950. Pp. 112. Price $2.25.

This is a monograph in the American Lecture Series on Physical Medicine. Its purpose is to present a brief survey of the present knowledge concerning the use of radiation for therapeutic purposes. The material is treated under four general headings: (1) History of Light Therapy; (2) Physics of Radiant Energy; (3) Infrared and Luminous Radiation and (4) Ultraviolet Radiation. The presentation of the material is somewhat uneven and, perhaps, too elementary and general for those particularly interested in the problem. This is especially true of the first part of the monograph. The last part of the book on ultraviolet radiation is more complete insofar as presentation of material, but again, many statements are made on controversial issues without documentation and adequate presentation of both sides of the story. Thus, the advisability of using ultraviolet radiation for "general tonic treatments" may be argued as may be its efficacy in preventing colds and alleviating anemias. On the other hand, the monograph contains a considerable amount of valuable advice and instruction on the use of radiation in therapy.

H. S. Mayerson, Ph. D.

Carbon Dioxide Therapy: By L. J. Meduna, M. D., Springfield, Charles C. Thomas, Publisher, 1950. Pp. 248. Illus. Price $5.00.

In this monograph, the author, Professor of Psychiatry at the University of Illinois, purports to develop a theory of psychoneuroses based on neu-

rophysiological principles in which carbon dioxide plays a significant role. He begins his book with a consideration that ordinary psychiatric treatment is too expensive for the average patient and that the carbon dioxide therapy which he has developed provides an inexpensive course of treatment which any physician can administer without trouble and without the use of "lingo" which he deems "absolutely unnecessary." He then proceeds to present a melange of references concerning the effects of carbon dioxide on functions of the nervous system without any particular order or coherence. Consideration of Lorente de No's experiments with 5 per cent carbon dioxide on peripheral nerve fiber activity is made. A consideration of the technic of treatment is then taken up, and this seems to consist of the use of a mixture of 30 per cent CO_2 and 70 per cent oxygen, which is inhaled by the patients for 25 to 35 respirations. These treatments are repeated from between 15 and 100 times, 30 treaments being the usual average. The effects produced are both motor and sensory following an initial period of anesthesia brought about by the large concentrations of CO_2. The book is filled with what seems to be unnecessarily excessive patient histories selected from a series of 100. Many of the treatments are stated to be effective resulting in cures of various psychoneuroses for periods of four years or more. However, these cures rarely seem to be convincing and a considerable number of relapses are reported. The author concludes with a long chapter on the basis of the theory which principally seems to involve the (entirely unproven) effects of CO_2 on positive and negative feedbacks in reverberating nervous system circuits. The scientific aspects of his discussions are often heavily interlarded with quotes from patients, flowery phraseology, and philosophical digressions. The proof of his theory is highly indirect, marked by complete absence of any controls, and completely contradicted by his use of anesthetic concentrations of CO_2 rather than the smaller excitatory concentrations.

L. M. N. Bach, Ph. D.

Enzymes, Growth and Cancer: By Van R. Potter, Ph. D. American Lectures in Physiology, No. 75, edited by R. F. Pitts, Springfield, Charles C. Thomas, Publisher, 1950. Pp. 64, Price, $1.85.

The text was developed while the author was Commonwealth Visiting Professor of Biochemistry at the University of Louisville, March 1947.

This book is not a text to be studied as a guide for the development of a workable knowledge of enzymology. It is rather a delightful essay to be read for its inspirational value to get at the spirit and purpose of enzyme studies. It was written to sell the idea that enzymology has an important contribution to make in the way of solving the enigma of cancer. A lay committee assigned to the disposal of funds for cancer research might well look into this essay. It is written in simple vein.

One suggestion is that research may show that cancer tissue contains certain enzyme systems overdeveloped and of a type that engenders unlimited growth. It is pointed out that a single chemical metabolite may be utilized in several alternate transition pathways. If certain of these became overdeveloped in cancerous tissue, growth might become unlimited. One of the best chapters is the last on inhibition and chemotherapy, wherein the hope is expressed that either competitive or irreversible type enzyme inhibitors might be found which will inhibit cancer growth but not other activities or normal body cells.

Walter S. Wilde, Ph. D.

Saw-Ge-Mah (*Medicine Man*) : By Louis J. Gariepy, M. D. St. Paul, Northland Press. 1950. Pp. 336. Price, $3.00.

This is the latest medical novel, and is written by a Detroit surgeon. Dr. Gariepy's extensive experience is duplicated in that of the hero of the book, first as a pharmacist, then as a general practitioner, a surgeon and organizer of a successful group practice. The problems of ethics and traditions of medical practice are well portrayed in the development of the story. The reviewer feels that the title is unfortunate and somewhat misleading, as the connection with Indian lore is not close, and the term is not well known nor easily remembered.

Mary Louise Marshall.

The Preparation of Photographic Prints for Medical Publication: By Stanley J. McComb, F. B. P. A. Springfield. Charles C. Thomas, 1950. Pp. 60. Illus. Price $2.00.

This informative illustrated text prepared by Stanley J. McComb of the Mayo Clinic, undoubtedly will prove of value to medical illustrators, physician-authors, as well as to amateur and commercial photographers who occasionally are called upon to photograph a medical subject. It is not intended as a text book but rather, as the author states, to offer suggestions "for the correction and improvement of some of the defects of medical photography commonly encountered." Concisely and clearly expressed the subject is broadly divided into: the preparation of photography, and the finishing of the photography for publication. Subdivided into separate chapters are little "lessons" in the preparation of the photography for publication, such as sharpness of focus, scale-size and position, backgrounds, lighting, emphasis, films, and the improvement of print quality. Each factor is briefly yet comprehensively outlined, and may be accepted as an authoritative guide for the promotion of better clinical photography. A bibliography is appended.

The need for physicians to be more critical of the photographic illustrations used is suggested by Mr. Ralph Creer, editor of this monograph.

VERA MOREL

Researches in Binocular Vision: By Kenneth N. Ogle, Ph. D., Division of Biophysical Research, Mayo Foundation, W. B. Saunders Company, Philadelphia, 1950. Illus. Pp. 345. Price $7.50.

In the foreword, Lancaster, who was associated with the work of the Dartmouth Eye Institute for a few years, wrote: "This book will immediately take its place as the authoritative source of the dependable basic truths so far discovered in the ever enlarging field of binocular vision." It is an authoritative source and concerns itself with basic truths which, however, are always relative and never absolute in a biological field in which anatomical, physiological, neurological, and psychological factors enter. The book by Ogle is a resume and compilation of the conceptions and researches of Ames, Ogle, and their collaborators at Dartmouth College.

It would be impossible to review adequately such a volume. It is divided into four parts: (1) The organization and sensory cooperation of the two retinas. (2) The fusional processes in binocular single vision. (3) The problems in binocular vision when changes are made in the relative magnifications of the images of the two eyes. (4) The experimental and theoretical bases for aniseikonia.

The chapters having to do with the phenomenon of fusion, Panum's fusional areas, fixation disparity, and fusion from peripheral retinal stimuli are among the most readable and stimulating parts of this outstanding contribution concerning binocular vision. The so-called induced effect receives much consideration. Dr. Ogle brings his presentation to a close by a thorough discussion of the experimental and theorectical bases for aniseikonia and, interestingly enough, captions the chapter in which aniseikonia is considered from both theoretical and clinical approaches "The stability of corresponding retinal points," and in the concluding paragraph states that "the results of this study would be evidence in favor of the Hering hypothesis of the innate and stable character of corresponding retinal elements."

To be sure the medically trained reader may experience some difficulty with the physical and mathematical approach and equations in contrast to the customary biological verbiage. But the effort to understand the material contained in Ogle's book is worth the effort to anyone in any wise interested in the things of vision. Now that the latest type of eikonometer with a simplified clinical technic is being made available, it is to be hoped that the so-called "practical and busy" ophthalmologist may persuade himself that it is worthwhile to comprehend and master some of the basic scientific work concerning binocular vision such as is disclosed in this volume.

JAMES ALLEN, M. D.

The Cerebral Circulation in Health and Disease: By Carl F. Schmidt, A. B., M. D. Springfield, Ill. Chas. C. Thomas Co., 1950. Pp. 78, Charts. Price $2.00.

On the whole, this monograph is a well organized review of the different aspects of the cerebral circulation and the difficult problem of its quantitative estimation. The author stresses the point

that the methods employed to investigate cerebral circulation of man must be "adequately quantitative" and that the observations have to be made in man himself, the latter due to the already established species differences. Particular emphasis is devoted to Kety's method and its application to the study of the human cerebral circulation in health and disease. Dr. Schmidt correctly points out that although the newly obtained information has served to shake confidence in concepts previously held, it is not yet extensive enough to allow the derivation of new ones. This book would be of special interest to those who, like the neurosurgeon and the neurologist, are confronted daily with the intricacies of the cerebral circulation of man in disease.

FRANCISCO GARCIA BENGOCHEA, M. D.

PUBLICATIONS RECEIVED

Meador Publishing Company, Boston: The Microkaryocytes, the Fourth Corpuscles and Their Functions, by K. G. Khorozian, A. B., M. S., M. D.

Oxford University Press, New York: Introduction to Surgery, by Virginia Kneeland Frantz, M. D., and Harold Dortic Harvey, M. D.